New Frontiers in Percutaneous Interventions

Nieuwe Ontwikkelingen in Percutane Interventies

Thesis

To obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof.dr. S.W.J. Lamberts

and in accordance with the decision of the Doctorate Board.

The public defence shall be held on
Wednesday the 27th of May 2009 at 11.45 o'clock

by

Emanuele Meliga
Born at Chivasso (Turin), Italy

DOCTORAL COMMITTEE

Promotor:	Prof. Dr. P.W. Serruys
Other members:	Prof. Dr. P.J.de Feyter
	Prof. Dr. W.J. van der Giessen
	Dr. P. Steendijk

TABLE OF CONTENTS

PART 2: INTERVENTION FOR CHRONIC TOTAL OCCLUSIONS

PART 3: INTERVENTIONS IN HIGH RISK PATIENTS

CHAPTER 1

INTRODUCTION

INTRODUCTION

In 1977 Andreas Gruntzig introduced a catheter-based therapy for the percutaneous management of patients with coronary artery disease. This became known as percutaneous transluminal coronary angioplasty (PTCA). Initially there were many skeptics and pessimists. The technology, however, evolved rapidly. With the advent of specialized catheters, guidewires, stents, and adjuvant pharmacotherapy, the indications for PTCA have expanded to include more urgent, comorbid cases and complex coronary disease. Furthermore, these innovations have largely solved earlier problems related to elastic recoil, dissection and restenosis of the treated segment. In particular, the introduction of stents with the capacity to elute drugs to the injured arterial wall has been shown to be an effective and overall safe approach to suppress intimal hyperplasia. The excellent results of DES in clinical trials and everyday clinical practice, in synergy with important improvements in adjuvant drug therapy, have expanded the indications of percutaneous coronary interventions even further. Within 10 years of its introduction, the number of PTCA procedures has surpassed the number of revascularizations accomplished by coronary artery bypass graft surgery.

Nowadays, treatment of unprotected left main coronary artery disease, chronic total occlusions, multi-vessel disease and the treatment of high-risk patients alike are considered the "new frontiers" of PCI. Part of this thesis relates to clinical results from registries and trials conducted in this subset of patients with complex coronary disease. The results demonstrate that PCI can be performed with encouraging outcomes both at short and long-term follow-up. However, there's still room for improvement – particular attention to techniques of intervention, materials and devices is warranted.

The progress made in PCI has also stimulated the development of techniques for the treatment of structural heart disease. New percutaneous techniques such as alcohol septal ablation and septal coil embolization to treat patients with hypertrophic cardiomyopathy are progressively entering clinical practice as safe and effective alternatives to surgery. Our results show that the introduction of a limited "therapeutic" infarction as a result of ethanol injection or the deployment of coils within the hypertrophied septal myocardium leads to localized thinning and regional contractile dysfunction, which expands the left ventricular outflow tract and thus reduces LVOT gradient and the resulting symptom.

Congestive heart failure treatment has today a "new frontier": cell transplantation therapy. The possibility of repairing and growing new myocardium within the necrotic tissue as a result of cell transplantation has been widely studied in both experimental and clinical conditions, using different types of cells with different delivery approaches. The characteristics of the ideal cell still remain to be defined, but it appears clear that, among the cells efficient in the treatment

of heart disease, cells that are autologous, nonembryonic, do not require culturing to obtain a therapeutic dose. These can be administered during the same procedure and may be logistically easier to use. In this thesis we report our preliminary experience with transplantation of autologous myoblast and adipose-derived stem cell in patients with ischemic heart disease and heart failure.

Similar to the materials and techniques used for interventions, there have been important advances in adjuvant pharmacotherapy. In particular, with PCI emerging as the new gold standard of care for ACS reperfusion therapy, new questions are arising about the best pharmaco-invasive strategy to limit the amount of myocardial damage occurring during the ischemia and early reperfusion periods. In this view, we tested a new type of hemoglobin-based oxygen carrier (HBOC) that, because of its ability to deliver oxygen directly to endothelium and tissues, may help to restore tissue oxygenation in post-stenotic areas during PCI. In this thesis we report the primary results of the proof-of-concept trial whereby HBOC was used in stable patients with coronary artery disease to assess its safety.

OUTLINE OF THE THESIS

Thesis – Part 1

The first part of the thesis examines the safety and efficacy of drug eluting stent implantation in patients with unprotected left main coronary artery disease. In chapter 2, we report the results of the DELFT Registry, an international multicenter registry that enrolled 358 consecutive patients with a minimum follow-up period of 3 years. Chapter 3 and 4 are sub-studies of the DELFT Registry and focus on the impact of stent selection on clinical outcomes (SP-DELFT) and on long-term clinical outcomes of diabetic patients with ULMCA disease treated with DES (D-DELFT). The comparison between percutaneous and surgical treatment of patients with left main disease is explored in chapter 5 while chapter 6 and 7 report findings on a limited and retrospectively selected group of patients who underwent PCI with sirolimus-eluting stent (SES) implantation and the comparison, in terms of clinical outcomes, between SES and bare metal stents (BMS). Chapter 8 is a large multicenter registry that explores the long-term safety of drug eluting stents and evaluates the occurrence of late and very late stent thrombosis following elective DES implantation in ULMCA stenosis. Finally, by a meta-analysis on 1278 patients, the risk-benefit balance of percutaneous DES implantation for ULMCA disease, in itself and in comparison with BMS-based PCI and CABG has been analyzed in chapter 9.

Thesis - Part 2

This section of the thesis examines percutaneous treatment of chronic total occlusions (CTO) in the drug-eluting stent era. Chapter 10 reports the long term follow up results of saphenous

vein graft recanalization compared to native vessel recanalization in a small population of post-CABG patients. Chapter 11 focuses on percutaneous retrograde approach, a novel and interesting technique that appears to be promising. So far however only limited data are available on this strategy. Finally the role of CTCA in the treatment of patients with CTOs is explored in chapter 12, a single center retrospective registry designed to identify potential predictors of success and to measure the risk-benefit ratio of this imaging technique performed in this particular subset of patients.

Thesis – Part 3

The safety and efficacy of DES in patients with high risk features has been evaluated in this thesis section. In chapter 13 the immediate and long-term results (12 months follow-up) of paclitaxel-eluting stent implanted in a high cardiovascular risk population with complex coronary lesions are reported while chapter 14 focuses on the short and long-term results of mutivessel PCI performed in patients with severe systolic dysfunction. The safety of an unrestricted use of DES has been questioned in several trials and independent meta-analysis, leading however to unclear or conflicting results. Chapter 15 provides a critical appraisal of recently published meta-analysis focusing on this issue. Finally, in chapter 16, the role of the Tandemheart (a percutaneous trans-septal ventricular assist device) in the context of high-risk percutaneous coronary interventions has been tested in a small population of emergent and elective patients.

Thesis – part 4

This section of the thesis focuses on the acute and chronic effects on left ventricular haemodynamics of percutaneous septal ablation for obstructive hypertrophic cardiomyopathy (HCM). The changes of left ventricular funcion were assessed by pressure-volume loops, dynamic data acquired by online pressure–volume signals obtained by a combined pressure-conductance catheter introduced into the left ventricle. Chapter 17 reports the acute changes in systolic and diastolic left ventricular function after alcohol induced septal myocardial ablation (PTSMA) and shed a light on the complex series of events that follow the procedure and that result in a new haemodynamic status. The chonic effects that PTSMA determines on systolic and diastolic left ventricular function are assessed and reported in chapter 18, while chapter 19 reports the acute results obtained in a patient with HCM treated with the novel method of septal coil embolization.

Thesis – part 5

This section describes cell characteristics, traditional and experimental delivery techniques and first clinical outcomes of cell transplantation performed in patients with cardiac heart failure secondary to ischemic heart disease. Chapters 20 and 21 describe characteristics, capabilities and the results derived from in-vitro and in-vivo studies of adipose-derived stem cells (ADSCs),

a new promising source of multi-potent stem cells. The APOLLO study, first in man trial conducted with ADSCs in patients with acute myocardial infarction is also described. Early clinical results of autologous skeletal myoblast used in the treatment of post-infarction injuries are reported in chapters 22 and 23 and 24 while chapter 25 focus on the early experience of cell transplantation procedures using a magnetic navigation supported delivery system.

Thesis – part 6

This last section of the thesis describes the early results obtained from the clinical use of Hemopure, an haemoglobin-based oxygen carrier that because of its ability to restore tissue oxygenation might play an important role in the setting of acute coronary syndromes. Chapter 25 describes the result of the COR-001 trial, a phase II, single center trial designed to test haemodynamic effects, safety and tolerability of intra-venous administration of Hemopure in patients scheduled for PCI. The encouraging results obtained in COR-001 trial led to the design of the COR-002 pilot trial, a single center, placebo-controlled, single blind trial conceived to test capabilities of Hemopure to restore and maintain myocardial oxigenation when injected in an ischemic territory.

SUMMARY AND CONCLUSIONS

Taking into consideration the published literature to date, the use of drug-eluting stents (DES) in patients with unprotected left main (ULM) coronary artery disease appears overall beneficial in comparison with bare metal stents (BMS). In particular, the use of DES is associated with significant reductions in target lesion revascularization, target vessel revascularization and MACE (major adverse cardiac events). In unspecified lesions, in-stent restenosis has been linked to the occurrence of acute coronary syndromes; but in the setting of left main restenosis, the risk of sudden cardiac death becomes a concern. Thus, the antiproliferative action of DES is of paramount importance in ULM lesions, and to date, DES should likely be recommended whenever percutaneous coronary interventions (PCI) for ULM is envisioned. Pooled analyses of registry data confirmed the early and mid-term safety and efficacy of DES implantation over BMS, under the premise that PCI is performed by experienced operators. Also, very-long-term follow-up of patients with ULM coronary artery disease treated with DES demonstrated a satisfactory rate in both single and composite outcomes. The progressive reduction of adverse events over time suggests

that DES are persistently effective. When PCI is performed electively, the event-free survival over a period of 3 years is excellent. This is independent of lesion location, stenting technique or type of drug-eluting stent used. When PCI is performed emergently, the favourable long-term clinical outcomes are hampered by lower event-free survival at shorter term follow-up.

It is interesting to note that in the in diabetic population with unprotected left main coronary artery disease the efficacy of DES is significantly influenced by the use of insulin. In fact, adverse outcomes comprising cardiac death, myocardial infarction, need of re-intervention and MACE was significantly increased in patients with insulin-dependent diabetes mellitus. The safety profile of drug-eluting stents appeared overall consistent with what has been reported in recent trials and registries focusing on selected patient/lesion subsets. The incidence of definite acute, sub-acute, late and very late stent thrombosis was low and not significantly related to cardiac death.

Notwithstanding the encouraging results obtained with DES for the treatment of ULM coronary artery disease, current guidelines still recommend surgical revascularization as the primary procedure. In all major institutions, current standard approach to patients presenting with significant ULM coronary artery disease is to have them evaluated by both interventional cardiologists and cardiac surgeons and to reach the decision to opt for PCI or surgery by consensus, on the basis of hemodynamic conditions, vessel / lesion characteristics, the presence of comorbidities and patient and/or referring physician preferences.

The results of the recently published SYNTAX trial represent a milestone and certainly will be taken into consideration in the upcoming guidelines. Guidelines are dynamic and in constant flux and have to be updated according to new evidences coming from clinical experience.

New-generation DES approved for clinical use, new technical strategies, new adjuvant therapies performed in the cath-lab, and prolonged dual antiplatelet treatment have significantly decreased the risk of adverse events (including late in-stent thrombosis), making PCI a safe and effective alternative to surgery in several high-risk subsets of patients.

In the context of chronic total occlusions both sirolimus-eluting stents and paclitaxel eluting stents have now been reported to be correlated with improved long-term clinical and angiographic outcomes compared with their BMS counterparts. Several studies reported high procedural success rates (particularly evident using the retrograde approach), single digit restenosis rates and no increase in stent thrombosis or late occlusion after DES implantation. Good clinical results were observed also in chronically occluded saphenous vein grafts. Though the benefit of DES in this lesion subset has not been formally evaluated (SVG lesions have been excluded from randomized trials), the available data coming from observational studies are encouraging. Remaining issues are the long-term safety and efficacy of DES in SVG lesions, considering that long-term events frequently result from the progression of other lesions in the vein. Regardless of the future progress in this field, we think that DES treatment currently is the best approach for SVG lesions. Despite extensive real-life use of DES in patients with multivessel disease, we cannot deny that sufficient data are still lacking. Rather than looking at the incidence of new revascularizations, which may be considered an acceptable "side effect" of any PCI strategy compared with CABG, we need to demonstrate equivalency or superiority in terms of MI and death evaluated no earlier than 5 years.

Coronary artery disease aside, advances in cardiovascular interventional techniques have allowed percutaneous treatment of conditions that either previously required open operations or have not been amenable to treatment.

Hypertrophic obstructive cardiomyopathy is a relatively common condition (prevalence of around 1 in 2000 persons) . The traditional method for the management of these patients has been the use of beta-blockers or calcium channel blockers, dual chamber pacing or surgical ventricular septal myectomy. Over the last decade, percutaneous approach to treatment of outflow tract gradient by ablating or creating a controlled infarction of the ventricular septum, has also been shown to be safe and effective. Percutaneous transluminal septal myocardial ablation (PTSMA) as well as septal coil embolization acutely reduce systolic function and improve diastolic function, maintaining cardiac output and stroke work. At long-term follow-up, the effects on general haemodynamics improve; in fact, while the LV–aortic gradient remaines low and active and passive LV diastolic properties are stable, myocardial contractility and systolic funcion improve. The indications for performing PTSMA are still being defined. Up to date, this novel technique may be a particularly attractive alternative in the elderly or those who because of significant co-morbidities cannot undergo /are refused by surgeons.

The enormous improvements in PCIs led to excellent rates of survival after an acute myocardial infarction. This increase has lead to a concomitant increase in the prevalence of post-infarction heart failure (HF) with at least a third of patients manifesting HF symptoms within a year. Currently, this increase is attributed both to limited efficacy of pharmacological agents at reducing left ventricle remodelling and HF exacerbations , and to underutilization of these drugs in general practice. Finally, post-infarction HF patients are surviving longer, in part because of a wider use of implantable cardioverter defibrillators. With the awareness that both tissues and bone marrow (BM) contain undifferentiated immature 'stem' cells normally used to replenish body tissues throughout life , and that these cells can be harvested and delivered to sites of injury, a new therapeutic option has emerged: the transplantation of stem or progenitor cells for functional repair or even regeneration of vasculature, acutely injured and/or failing myocardium or previously irreversibly damaged heart – giving hope for cell-mediated prevention, treatment and possibly even cure of CVD. Trials performed to date have focused on the use of BM-MNCs, EPCs, MSCs and other cells throughout the continuum of cardiovascular disease, from advanced coronary atherosclerosis to end-stage HF, with the most patients treated following AMI. Three recent meta-analyses suggest that BM-MNCs provide statistically significant yet small (in clinical terms) benefit when administered post-AMI. However, on close examination of individual studies, the outcomes are discrepant. Whether the discrepancies represent differences in disease context, patient population, cell type and dose or some other factors remains to be resolved. In other words, 7 years after the initiation of the first study we still have as many (or more) questions as answers.

Among the variety of cells studied, autologous skeletal myoblasts are one of the most encouraging cell sources for cardiac repair. They are of their autologous origin, the ability to

be amplified in vitro, and have high proliferative potential resistance to ischaemia and pre-clinical efficacy. These characteristics have led clinical investigators to evaluate the effect of transplanted autologous myoblasts in patients with post-infarction heart failure. Myoblasts differentiate into myotubes and maintain muscle properties when transplanted into an infarct area. The direct contribution

of these engrafted cells in improving systolic function was noticed in several studies that indicated a

positive effect of skeletal myoblasts on myocardial contractility lasting over time and correlating with the number of implanted cells.

Recently it has been shown that adipose tissue, in addition to committed adipogenic, endothelial progenitor cells and pluripotent vascular porgenitor cells, contains multipotent cells, similar to MSCs. ADSC have extensive proliferative capacity, are able to undergo differentiation along both mesenchymal lineages and non-mesenchymal lineages, are known to secrete a large number of angiogenesis-related cytochines and display and immunoprivileged behavior.

This finding has generated major interest because, in contrast to bone marrow, large quantities of adipose tissue can be easily harvested with minimal morbidity, making it an appealing source for cell therapy. The APOLLO trial will provide important data about the safety and efficacy of these cells in humans, providing an essential insight on what could be their role in the treatment of cardiovascular disease.

PART 1

INTERVENTION FOR THE LEFT MAIN CORONARY ARTERY STENOSIS

CHAPTER 2

LONGEST AVAILABLE CLINICAL OUTCOMES AFTER DRUG-ELUTING STENT IMPLANTATION FOR UNPROTECTED LEFT MAIN CORONARY ARTERY DISEASE: THE DELFT (DRUG ELUTING STENT FOR LEFT MAIN) REGISTRY

CLINICAL RESEARCH Interventional Cardiology

Longest Available Clinical Outcomes After Drug-Eluting Stent Implantation for Unprotected Left Main Coronary Artery Disease

The DELFT (Drug Eluting stent for LeFT main) Registry

Emanuele Meliga, MD,*† Hector Manuel Garcia-Garcia, MD, MSc,* Marco Valgimigli, MD, PhD,‡ Alaide Chieffo, MD, PhD,§ Giuseppe Biondi-Zoccai, MD,† Andrew O. Maree, MD,‖ Stephen Cook, MD,¶ Lindsay Reardon, MD,‖ Claudio Moretti, MD,† Stefano De Servi, MD,# Igor F. Palacios, MD, FACC,‖ Stephen Windecker, MD,¶ Antonio Colombo, MD, FACC, FESC,§ Ron van Domburg, PhD,* Imad Sheiban, MD,† Patrick W. Serruys, MD, PhD, FACC, FESC*

Rotterdam, the Netherlands; Turin, Ferrara, and Milan, Italy; Boston, Massachusetts; and Bern, Switzerland

Objectives The purpose of this study was to investigate the long-term safety and efficacy of percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation for unprotected left main coronary artery (ULMCA) disease.

Background Long-term clinical outcomes after DES implantation for ULMCA disease have not yet been ascertained.

Methods From April 2002 to April 2004, 358 consecutive patients who underwent PCI with DES implantation for de novo lesions on ULMCA were retrospectively selected and analyzed in 7 European and U.S. tertiary care centers. No patients were excluded from the analysis, and all patients had a minimum follow-up of 3 years.

Results Technical success rate was 100%. Procedural success rate was 89.6%. After 3 years, major adverse cardiovascular events (MACE)-free survival in the whole population was 73.5%. According to the Academic Research Consortium definitions, cardiac death occurred in 9.2% of patients, and reinfarction, target lesion revascularization (TLR), and target vessel revascularization (TVR) occurred in 8.6%, 5.8%, and 14.2% of patients, respectively. Definite stent thrombosis occurred in 2 patients (specifically at 0 and 439 days). In elective patients, the 3-year MACE-free survival was 74.2%, with mortality, reinfarction, TLR, and TVR rates of 6.2%, 8.3%, 6.6%, and 16%, respectively. In the emergent group the 3-year MACE-free survival was 68.2%, with mortality, reinfarction, TLR, and TVR rates of 21.4%, 10%, 2.8%, and 7.1%, respectively.

Conclusions Routine DES implantation in ULMCA disease seems encouraging, with favorable long-term clinical results. (J Am Coll Cardiol 2008;51:2212–9) © 2008 by the American College of Cardiology Foundation

Preliminary trial results confirmed that implantation of drug-eluting stents (DES) to treat unprotected left main coronary artery (ULMCA) lesions is a feasible and relatively safe approach in appropriately selected patients (1–5). However, coronary artery bypass grafting (CABG) still remains the treatment of choice in this cohort (6,7). Lack of long-term follow-up (>2 years) data and increasing awareness of the potentially fatal consequences of stent thrombosis (ST) or in-stent restenosis in this patient subset is proving a significant deterrent to offer percutaneous coronary intervention (PCI) with DES implantation in patients amenable to CABG (8–12).

The main goal of this study was to generate the longest available follow-up data and identify associated predictors for adverse outcomes in patients undergoing intervention with DES for ULMCA lesions in a "real-world" setting with an international, multicenter, retrospective registry design.

Methods

Population. Between April 2002 and April 2004, consecutive patients who underwent PCI with a sirolimus-eluting

From the *Department of Interventional Cardiology, Erasmus Medical Centre, Erasmus University, Rotterdam, the Netherlands; †Department of Interventional Cardiology, S. Giovanni Battista Hospital, University of Turin, Turin, Italy; ‡Department of Interventional Cardiology, S. Anna Hospital, University of Ferrara, Ferrara, Italy; §Department of Interventional Cardiology, S. Raffaele Hospital, Milan, Italy; ‖Department of Interventional Cardiology, Massachusetts General Hospital, Boston, Massachusetts; ¶Department of Interventional Cardiology, University Hospital, Bern, Switzerland; and the #Department of Cardiovascular Diseases, Ospedale Civile di Legnano, Legnano (Milan) Italy.

Manuscript received November 6, 2007; revised manuscript received February 28, 2008, accepted March 4, 2008.

stent (SES) or paclitaxel-eluting stent (PES) for de novo lesions in the ostium, shaft, or distal ULMCA were identified retrospectively and analyzed in 7 European and U.S. tertiary health care centers. All patients had confirmed myocardial ischemia related to ULMCA disease.

Patients were stratified into risk classes with the European System for Cardiac Operative Risk Evaluation (EuroSCORE) (13) (Table 1). Subjects with a EuroSCORE >6 were defined as high risk, and those with a EuroSCORE >9 as very high risk. Additional information about the risk of mortality and morbidity was generated with the Society of Thoracic Surgeons (STS) score. Data analysis was performed with the approval of the institutional ethics committees of the hospitals and/or universities involved.

Procedures and medications. All interventions were performed according to concurrent guidelines. Angioplasty strategy, use of periprocedural glycoprotein IIb/IIIa inhibitors, route of arterial access, pre-dilation devices, intravascular ultrasound guidance, and prophylactic intra-aortic balloon pump use was at the discretion of the operator.

All elective patients were pre-treated with aspirin, clopidogrel (75 mg/day 3 days before the procedure or 300-mg loading dose), and low-molecular-weight or unfractionated heparin (administered in the cath lab, before guidewire insertion). Heparin was titrated to maintain an activated clotting time >250 s. In general, patients who underwent emergent PCI received oxygen adjusted according to blood saturation before cardiac catheterization, aspirin 100 to 160 mg chewed, a 300-mg loading dose of clopidogrel, and intravenous heparin to maintain the activated clotting time >250 s.

Complete revascularization was attempted in all patients at the time of the index PCI. Significant lesions that were not treated during the index procedure were staged and treated generally within 1 month.

After the procedure, all patients were prescribed lifelong aspirin (75 to 100 mg/day), and prolonged (at least 6 months) dual antiplatelet therapy of aspirin + clopidogrel or aspirin + ticlopidine was recommended. Repeated revascularization was only performed if there was either symptom recurrence or inducible ischemia related to the ULMCA disease.

Angiographic follow-up was performed according to institutional guidelines, usually between 6 and 9 months after the procedure.

Definitions. Technical success was defined as the successful deployment of the stent(s) in the target lesion.

Procedural success was defined as left main revascularization with a ≤30% residual diameter stenosis by quantitative coronary angiography, without major procedural or post-procedural adverse events (death, myocardial infarction [MI], emergency target vessel revascularization, or acute ST).

Hemodynamic instability (HI) was defined as the presence of hypotension (systolic blood pressure <90 mm Hg) associated with signs of global or regional hypoperfusion, without meeting all of the criteria for cardiogenic shock.

Emergency PCI was defined as a PCI in patients treated before the beginning of the next working day with cardiogenic shock, ST-segment elevation myocardial infarction, or unstable angina associated with signs of progressive HI unresponsive to standard medical treatment.

Death was classified as either cardiac death (CD) or noncardiac, according to the Academic Research Consortium (ARC) definitions (14). Deaths that could not be classified were considered cardiac.

Target lesion revascularization (TLR) was defined as any repeat percutaneous intervention of the target lesion or other complication of the target lesion. The target lesion was defined as the treated segment from 5 mm proximal to the stent and to 5 mm distal to the stent.

Table 1 The Additive EuroSCORE System

Patient factors	
Age (yrs)	0–6
Gender (female)	1
Chronic pulmonary disease	1
Extracardiac arteriopathy	2
Neurological dysfunction	2
Previous cardiac surgery	3
Serum creatinine >200 μmol/l	2
Active endocarditis	3
Critical preoperative state	3
Cardiac factors	
Unstable angina	2
LV dysfunction moderate or LVEF 30%–50%	1
LV dysfunction poor or LVEF <30%	3
Recent myocardial infarct	2
Pulmonary hypertension	2
Operation factors	
Emergency	2
Other than isolated CABG	2
Surgery on thoracic aorta	3
Postinfarct septal rupture	4

For more information on the European System for Cardiac Operative Risk Evaluation (EuroSCORE) see Nashef et al. (13).

CABG = coronary artery bypass grafting; LV = left ventricular; LVEF = left ventricular ejection fraction.

Abbreviations and Acronyms

AMI = acute myocardial infarction

BMS = bare-metal stent(s)

CABG = coronary artery bypass grafting

CD = cardiac death

DES = drug-eluting stent(s)

EF = ejection fraction

EuroSCORE = European System for Cardiac Operative Risk Evaluation

HI = hemodynamic instability

IDDM = insulin-dependent diabetes mellitus

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

PES = paclitaxel-eluting stent(s)

SES = sirolimus-eluting stent(s)

ST = stent thrombosis

TLR = target lesion revascularization

TVR = target vessel revascularization

ULMCA = unprotected left main coronary artery

Target vessel revascularization (TVR) was defined as any repeat PCI of any segment of the target vessel, defined as the entire major coronary vessel proximal and distal to the target lesion, including upstream and downstream branches and the target lesion itself.

A major adverse cardiac event (MACE) was defined as the occurrence of CD, nonfatal MI, or TVR during the follow-up period.

Definite, probable, and possible stent thromboses were determined according to the ARC definitions (14). Stent thrombosis was defined as acute, subacute, late, and very late if the event occurred within 24 h, 30 days, <1 year, or >1 year, respectively, after the procedure.

Myocardial infarction was defined as a creatine kinase-MB mass increase >3 times the upper limit of normal, associated with chest pain lasting >30 min or with new evident electrocardiographic changes.

Data collection and follow-up. All data relating to hospital admissions, procedures, and in-hospital outcomes were collected in each center with the hospital recording network. Information regarding clinical status was collected at clinic visits and by telephone interview. When the patient was not reachable, the information was sought from the referring physician, hospital electronic database, or Municipal Civil Registries. The data collection was carried out with a dedicated electronic case report form (CRF). All of the explored variables in the CRF were defined and number-coded before the CRF was sent to each participating center. At 3 years the clinical follow-up was 100%. This protocol was approved by the hospital ethics committees and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

Statistical analysis. Continuous variables are expressed as mean ± SD, and categorical variables are expressed as counts and percentages.

The MACEs are reported hierarchically. Survival curves were generated by the Kaplan-Meier method, and survival among groups was compared with the log-rank test.

Bivariate and multivariate analyses were performed to identify independent predictors of adverse events. Specifically, all variables significantly associated with the clinical event of interest on bivariate analysis ($p < 0.10$) were entered into subsequent models. After appropriate checks for underlying assumptions, multiple variable Cox proportional hazard analyses were then performed, with the enter method for all pertinent covariates. Results of multiple variable Cox analyses are reported as hazard ratios with 95% confidence intervals and p values. All analyses were performed with SPSS version 12 statistical software (SPSS Inc., Chicago, Illinois). A 2-tailed p value < 0.05 was considered significant for hypothesis testing.

Results

Baseline characteristics. Baseline clinical characteristics are shown in Table 2.

Table 2 Baseline Clinical Characteristics

Age (yrs)	66.1 ± 11.2
Men	264 (73.7)
BMI (kg/m^2)	26.7 ± 4.7
Arterial hypertension	238 (66.5)
Hypercholesterolemia	230 (64.2)
Current smoking	120 (33.5)
Diabetic patients	108 (30.2)
IDDM	58 (16.2)
NIDDM	50 (14)
Familial risk factor	93 (26)
Previous AMI	162 (45.3)
Previous PCI	108 (30.2)
Previous CABG	68 (18.9)
Diagnosis at admission	
Stable angina	158 (44.1)
Unstable angina	150 (41.9)
AMI	30 (8.4)
AMI + shock	10 (2.8)
Silent ischemia	10 (2.8)
LVEF	48.6 ± 12.8
EuroScore	6.4 ± 4.1
>6	73 (20.4)
>9	111 (31)
Average elective	5.7 ± 3.8
Average emergent	9.9 ± 3.5

Values given as n (%).

AMI = acute myocardial infarction; BMI = body mass index; IDDM = insulin-dependent diabetes mellitus; NIDDM = noninsulin-dependent diabetes mellitus; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

Patients (n = 358) of mean age 66.1 ± 11.2 years and mean body mass index 26.7 ± 4.7 kg/m^2 were treated for ULMCA stenosis with DES. During the same period, a total of 680 patients with significant ULMCA disease underwent CABG in the 7 participating centers. Men comprised 73.7% of the cohort. One hundred eight patients (30.2%) were diabetic. Of these, 58 (16.2%) had insulin-dependent diabetes mellitus (IDDM) and 50 (14%) had non-IDDM. Almost one-half of the patients (162, 45.3%) had a prior history of acute myocardial infarction (AMI), 108 (30.2%) had had a previous PCI, and 68 (18.9%) had previously undergone CABG. The most common admission diagnosis was stable angina (158, 44.1%), followed by unstable angina (150, 41.9%), AMI (30, 8.4%), cardiogenic shock (10, 2.8%), and silent ischemia (10, 2.8%). The mean ejection fraction (EF) was 48.6 ± 12.8%, and the mean EuroSCORE was 6.4 ± 4.1.

In the emergent subgroup, mean EuroSCORE was 9.9 ± 3.5, and the most common diagnosis on admission was AMI (n = 31, 44.3%), followed by unstable angina with HI (n = 29, 41.4%) and cardiogenic shock (n = 10, 14.3%).

The risk of mortality and morbidity or mortality calculated by Society of Thoracic Surgeons (STS) score were 1.6 ± 0.7% and 13.5 ± 4.1% in the elective group and 22.3 ± 6.4% and 46 ± 11.3% in the emergent group, respectively.

Procedural and angiographic characteristics. Procedural and angiographic characteristics are shown in Table 3. In

Table 3 Angiographic and Procedural Characteristics

Emergent PCI	70 (19.6)
UA with HI	29 (41.4)
AMI	31 (44.3)
CS	10 (14.3)
Lesion location	
Ostium/shaft	94 (26.3)
Distal	264 (73.7)
DES	
Cypher	195 (54.5)
Taxus	163 (45.5)
Approach	
Single stent	203 (56.7)
Multiple stent	155 (43.3)
Stenting technique	
Provisional	203 (56.7)
V-stenting	30 (8.3)
T-stenting	14 (3.9)
Crushing	95 (26.5)
Culotte	16 (4.4)
Multivessel treatment	182 (50.8)
Stents/patient	1.47 (529/358)
Stent diameter, mm	3.23 ± 0.31
Stent length, mm	17.3 ± 6.7
Pre-dilation	169 (47.2)
Thrombectomy	5 (1.4)
Cutting	28 (7.8)
Rotablator	8 (2.2)
Atherectomy	5 (1.4)
Post-dilation	188 (52.5)
Maximal inflation pressure, atm	16.8 ± 2.8
Final kissing	133 (37.2)
Bigger balloon size, mm	3.53 ± 0.55
IABP	50 (13.9)
Post-procedural RVD, mm	3.71 ± 0.54
Post-procedural MLD, mm	3.32 ± 0.57
TIMI flow at baseline	
0–1	61 (17)
2	24 (6.7)
3	273 (76.3)
Angiographic follow-up	255 (71.2)

Values given as n (%).

AMI = acute myocardial infarction; CS = cardiogenic shock; DES = drug-eluting stent; HI = hemodynamic instability; IABP = intra-aortic balloon pump; MLD = minimal lumen diameter; RVD = reference vessel diameter; TIMI = Thrombolysis in Myocardial Infarction; UA = unstable angina.

brief, elective PCIs comprised 80.4%, and emergent PCIs comprised 19.6% of procedures. Sirolimus-eluting stents were deployed in 54.5% of patients, and paclitaxel-eluting stents were deployed in 45.5%. Baseline Thrombolysis In Myocardial Infarction (TIMI) flow assessment in the ULMCA was 0 to 1 in 17% of patients, 2 in 6.7%, and 3 in 76.3%. Lesions were more frequently distal (73.7%) than ostial/shaft (26.3%). The ULMCA was treated with multiple stents in 43.3% of cases, and crush stenting (26.5%) was favored over V-stenting (8.3%), Culotte (4.4%), and T-stenting (3.9%) techniques. Mean stent diameter was 3.23 ± 0.31 mm, mean stent length was 17.3 ± 6.7 mm, and the stents/patient ratio was 1.47. Mean post-procedural reference vessel diameter was 3.71 ± 0.54 mm, and mean minimal lumen diameter was 3.32 ± 0.57 mm. Multivessel treatment was performed in approximately one-half of the population (50.8%).

Procedural and in-hospital outcomes. Procedural and in-hospital outcomes are summarized in Table 4. Technical success was achieved in 100% of cases and procedural success in 89.6%. Overall, the in-hospital death rate was 3%, and the post-procedural MI rate was 7.3%. Urgent TLR was required in 0.3% and urgent TVR in 0.8%, and the incidence of MACE was 11.1%. In-hospital death and MACE were significantly more likely after emergent rather than elective procedures (12.8% vs. 0.7%, $p < 0.001$, and 22.8% vs. 8.3%, $p < 0.001$, respectively).

Table 4 Incidence of Adverse Events in the Whole Population, in Elective Patients, and in Emergent Patients

	Overall (n = 358)	Elective (n = 288)	Emergent (n = 70)	p Value
In-hospital				
CD	11 (3)	2 (0.7)	9 (12.8)	<0.001
MI	26 (7.2)	20 (6.9)	6 (8.6)	0.39
TLR	1 (0.3)	0 (0)	1 (1.4)	0.19
TVR	3 (0.8)	2 (0.7)	1 (1.4)	0.48
MACE	40 (11.1)	24 (8.3)	16 (22.8)	<0.001
30 days				
CD	12 (3.3)	2 (0.7)	10 (14.3)	<0.001
MI	26 (7.2)	20 (6.9)	6 (8.6)	0.39
TLR	2 (0.6)	1 (0.3)	1 (1.4)	0.35
TVR	3 (0.8)	2 (0.7)	1 (1.4)	0.48
MACE	41 (11.4)	24 (8.3)	17 (24.3)	<0.001
6 months				
CD	17 (4.7)	5 (1.7)	12 (17.1)	<0.001
MI	26 (7.2)	20 (6.9)	6 (8.6)	0.39
TLR	9 (2.5)	8 (2.7)	1 (1.4)	0.44
TVR	21 (5.8)	18 (6.2)	3 (4.3)	0.38
MACE	64 (17.8)	43 (14.9)	21 (30)	0.003
1 yr				
CD	24 (6.7)	11 (3.8)	13 (18.6)	<0.001
MI	27 (7.5)	21 (7.3)	6 (8.6)	0.43
TLR	14 (3.9)	13 (4.5)	1 (1.4)	0.2
TVR	36 (10)	32 (11.1)	4 (5.7)	0.12
MACE	87 (24.3)	64 (22.2)	23 (32.9)	0.046
3 yrs				
CD	33 (9.2)	18 (6.2)	15 (21.4)	<0.001
MI	31 (8.6)	24 (8.3)	7 (10)	0.4
TLR	21 (5.8)	19 (6.6)	2 (2.8)	0.18
TVR	51 (14.2)	46 (16)	5 (7.1)	0.037
MACE	115 (32.1)	88 (30.5)	27 (38.5)	0.126
>3 yrs				
CD	38 (10.6)	20 (6.9)	18 (25.7)	<0.001
MI	32 (8.9)	24 (8.3)	8 (11.4)	0.27
TLR	22 (6.1)	19 (6.6)	3 (4.3)	0.34
TVR	55 (15.3)	47 (16.3)	8 (11.4)	0.2
MACE	125 (34.9)	91 (31.6)	34 (48.5)	0.006

Values given as n (%).

CD = cardiac death; MACE = major adverse cardiac events; MI = myocardial infarction; TLR = total lesion revascularization; TVR = total vessel revascularization.

Follow-up clinical outcomes. Follow-up clinical outcomes at 30 days, 1 year, and 3 years are shown in Table 4 and in Figure 1. Patients were followed up for at least 36 months (range 36 to 60.2 months). Angiographic follow-up was available in 71.2% of patients.

At 30 days, the incidence of CD was 3.3% and was significantly higher in emergent procedures when compared with elective (14.3% vs. 0.7%; $p < 0.001$). The incidence of MI, TLR, and TVR was 7.2%, 0.6%, and 0.8%, respectively. A MACE occurred in 11.4% and significantly more frequently with emergent procedures compared with elective (24.3% vs. 8.3%; $p < 0.001$).

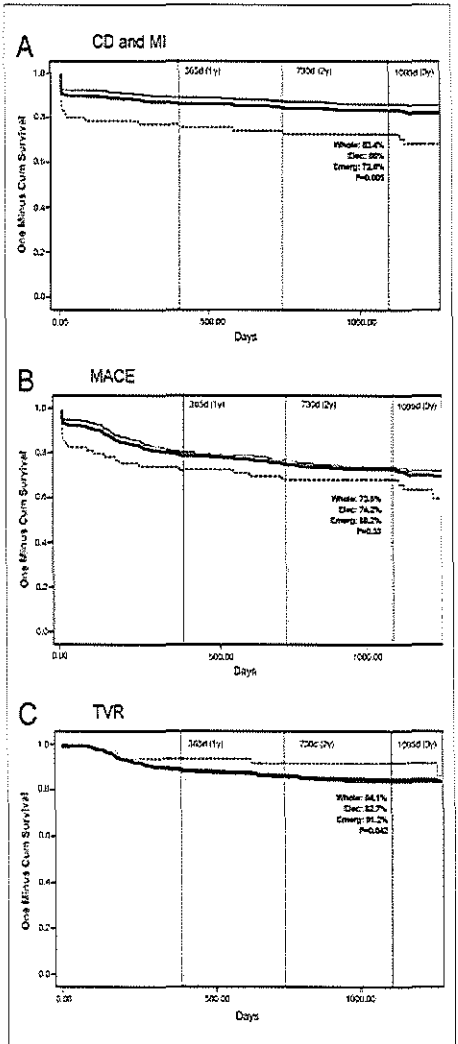


Figure 1 Kaplan-Meier Curves

(A) Freedom from cardiac death (CD) and myocardial infarction (MI). (B) Freedom from major adverse cardiac events (MACE). (C) Freedom from target vessel revascularization (TVR). **Solid lines** = elective patients (Elec); **solid bold lines** = whole population (Whole); **dashed lines** = emergent patients (Emerg). The p value represents the difference between the elective and the emergent groups.

At 1 year, the incidence of CD was 6.7% and the incidence of MI, TLR, and TVR were 7.5%, 3.9%, and 10%, respectively. A MACE occurred in 24.3% of patients. The association with CD and MACE remained significant for emergent cases when compared with elective procedures (18.6% vs. 3.8%, $p < 0.001$, and 32.9% vs. 22.2%, $p = 0.046$).

The 3-year incidence of CD was 9.2%, and the incidence of MI, TLR, and TVR were 8.6%, 5.8%, and 14.2%, respectively. A MACE occurred in 32.1% of cases. Occurrence of CD (21.4% vs. 6.2%; $p < 0.001$) but not MACE (38.5% vs. 30.5%; $p = 0.126$) remained significantly higher in emergent cases relative to elective cases.

Data derived from the Kaplan-Meier survival curves are reported in Figure 1. Of note, the great majority of events occurred within 1 year in both groups of patients (72.7% and 85.4% in the elective and in the emergent group, respectively), whereas the cumulative event rate tended to stabilize over time.

Stent thrombosis. The ST events are described in Table 5.

Definite ST occurred in 2 (0.6%) patients at 0 and 439 days. Probable ST occurred in 4 (1.1%) patients, and possible ST occurred in 16 (4.4%) patients. Concerning the definite ST, acute ST occurred in 1 patient (0.3%) and very late in 1 (0.3%). No subacute and late ST occurred.

Acute ST occurred in a patient with acute coronary syndromes who underwent emergent PCI and received a single DES for a significant ostial lesion. Very late ST occurred in a patient with stable angina who underwent an elective PCI and received 3 DES for a significant lesion located in the distal left main. One-year dual antiplatelet therapy was recommended and thus, at the time of the ST event, was not ongoing. Both events occurred in patients who were classified as very-high-risk patients (EuroSCORE 9 and 11). No case of definite ST resulted in CD.

Multivariable analyses. Results of multivariable analyses are presented in Table 6 and Online Tables 1 and 2. Of note, the following were identified as independent predictors of cardiac death (CD): age, shock, EuroSCORE, and impaired EF (<50%). The IDDM and EuroSCORE were significant predictors of MACE and IDDM; impaired EF and multiple stenting predicted the need for TVR.

Discussion

The main findings of this report are the following: there was a high clinical and procedural success rate associated with DES insertion to treat ULMCA stenosis. Follow-up at 30 days, 6 months, and 3 years demonstrated a satisfactory rate of MACE. Of note, the great majority of adverse events occurred within the first year, whereas thereafter, the event rate tended to stabilize over time, suggesting a prolonged efficacy of DES over time. When elective and emergent PCI

Table 5 ST According to ARC Definitions

	Acute (<24 h)	Subacute (<30 days)	Late (<1 yr)	Very-Late (>1 yr)	Total
Definite ST	1 (0.3)	0 (0)	0 (0)	1 (0.3)	2 (0.6)
Probable ST	1 (0.3)	2 (0.6)	0 (0)	1 (0.3)	4 (1.1)
Possible ST	0 (0)	0 (0)	8 (2.2)	8 (2.2)	16 (4.4)
Total	2 (0.6)	2 (0.6)	8 (2.2)	10	22 (6.1)

Values given as n (%).
ARC = Academic Research Consortium; ST = stent thrombosis.

were compared, the former was associated with excellent 3-year event-free survival, whereas emergent PCI was associated with a lower but satisfactory clinical success rate. In terms of safety, there were only 2 cases of definite thrombosis that occurred in a very-high-risk patient. Overall, the ST rates were lower than in other lesion subsets (15).

General population and elective patients. Very-long-term safety and efficacy data for DES used to treat ULMCA disease in unselected consecutive patients are lacking. Thus, it is difficult to put into perspective the results of our report.

In the bare-metal stent (BMS) era, patients with ULMCA disease treated percutaneously were carefully selected. Lee et al. (16) reported on 5-year follow-up patients (n = 187) with ULMCA disease that was treated percutaneously with BMS. All were elective and had normal EF and a low rate of distal left main involvement (37%). Moreover, when compared with our population, patients were significantly younger (56 ± 11 years vs. 66 ± 11 years) and had a lower incidence of hypertension (27% vs. 66%), hypercholesterolemia (30% vs. 64%), and diabetes (20% vs. 30%), and significantly higher post-procedural minimal lumen diameter (4.1 ± 0.7 mm vs. 3.3 ± 0.57 mm). A crude comparison of the 2 populations after 3-year follow-up shows a higher cumulative incidence of CD (9.2% vs. 2.3%) and lower MACE-free survival (73.5% vs. 77.5%) in our series relative to that of Lee et al. (16). After exclusion of emergent patients (n = 70) and elective patients with an EF <50% (n = 80), a repeat comparison of our cohort with that of Lee et al. (16) demonstrates a similar cumulative incidence of CD (1.2% vs. 2.3%) and rate of MACE-free survival (77.7% vs. 77.5%). Thus, treatment of ULMCA in higher-risk populations with DES achieves results similar to that of lower-risk populations treated with BMS.

Lee et al. (16) reported a cumulative incidence of TLR after 1 and 3 years (TVR rate not reported) of 18.8% and 20.7%, respectively, whereas the incidence in our comparable subpopulation was 2.9% and 6.7%, respectively. These data are consistent with published results from DES versus BMS randomized trials (17–20).

Recent reports (1,5) of DES use to treat ULMCA in selected populations showed considerable variability in the incidence of CD (range 0% to 11%), TVR (range 6% to 15%), and MACE (range 2% to 26%) at 1-year follow-up. This variability most likely represents relative differences in the inclusion and exclusion criteria applied and a lack of long-term follow-up results and makes comparison difficult. A study conducted by Sheiban et al. (3) reported excellent results in terms of death, TVR, and MACE at 12 and 24 months in a population of 85 consecutive unselected patients who underwent ULMCA revascularization with DES. Although from a small population derived from a single center, these results are in line with ours and suggest that DES implantation in "real-world" patients with ULMCA disease is both feasible and safe and effective over time.

The survival curve showed that the main occurrence of adverse events—in terms of CD, MI, and TVR—was within the first 12 months, whereas thereafter, the curves showed a progressive tendency to flatten. In the overall population and in the elective subgroup, the 79.7% and 76.5% of all CDs and MIs, respectively, occurred within the first year of follow-up. Consistently, 70.9% (69.3% in the elective subgroup) of all TVRs and 75.7% (72.7% in the elective group) of all MACEs occurred within the first year, suggesting that the enhanced antiproliferative effect of DES is persistent and that, in this specific population, the so-called "catch-up" phenomenon seems not to occur at this point in time in this population. This is in line with the 2-year reports available so far (3).

In addition, our results suggest that treatment of elective patients with ULMCA disease with DES does not differ significantly from treatment of those with multivessel disease in terms of MACE. In fact, our findings are in line with those reported by Morice et al. (21) in the REALITY (Sirolimus versus Paclitaxel-eluting Stents in De Novo Coronary Artery Lesions) trial in 2006. The noncumulative incidence of MACE (matched for our definition of MACE) at 1-year follow-up in the REALITY trial was 14.75% (14.6% in the

Table 6 Multivariable Predictors of Freedom From Adverse Clinical Events

Variable	CD	MACE	TVR
Age	1.06 (1.01–1.11), p = 0.010	—	—
IDDM	—	2.85 (1.29–6.17), p = 0.009	2.92 (1.60–5.30), p < 0.001
Shock	11.0 (1.88–63.9), p = 0.008	—	—
EuroSCORE	1.15 (1.01–1.31), p = 0.046	1.10 (1.02–1.19), p = 0.014	—
LVEF (<50%)	—	—	1.03 (1.01–1.05), p = 0.050
Multiple stenting	—	—	4.51 (1.07–19.0), p = 0.040

Only significant (p < 0.05) predictors are reported, as hazard ratios (95% confidence intervals), p values.
EuroSCORE = European System for Cardiac Operative Risk Evaluation; IDDM = insulin-dependent diabetes mellitus; LVEF = left ventricular ejection fraction; other abbreviations as in Table 4.

SES group; 14.9% in the PES group) compared with 22.2% in our cohort. Furthermore, the incidence of CD, MI, and TVR (matched with our definition of TVR) was 1.25%, 5.55%, and 7.95%, respectively, in the REALITY trial (average of the SES and PES groups) versus 3.8%, 7.3%, and 11.1% in our report.

Diabetes mellitus, multiple stenting, and impaired EF were found to be independent predictors of TVR in our population, which is consistent with a similar published analysis in other coronary lesion subsets (22).

Emergency PCI. Percutaneous treatment of ULMCA disease in an emergent setting is not supported by current and prior American College of Cardiology/American Heart Association (ACC/AHA) guidelines for percutaneous coronary intervention (7) and reflects the lack of available data for the acute and long-term safety and efficacy of PCI in this particular subset of patients.

In the present study, at 30 days the incidence of MACE was significantly higher than in the elective group (24.3% vs. 8.3%, $p < 0.001$). At 3-year follow-up, however, the difference in MACE-free survival between the elective and the emergent group was only 6% (74.2% vs. 68.2%, respectively, $p = 0.33$). It is noteworthy that although TVR was over-represented among adverse events at 3-year follow-up in the elective group (52.3% of all adverse events), CD represented the major component in the emergent group (55.5% of all adverse events). Thereby, the 3-year incidence of TVR was shown to be significantly lower in the emergent group ($p = 0.04$), whereas conversely the incidence of CD and MI at 3 years was found to be significantly higher in these patients when compared with the elective group ($p = 0.005$).

As in the elective population, the survival curve showed that the vast majority of adverse events occurred within the first year of follow-up. In these patients, 86.6% of all CDs and MIs, 80.2% of all TVRs, and 85.4% of all MACEs occurred in the first 12 months. The incidence of CD and MI at 12 months was significantly lower in the elective PCI population compared with the emergent PCI population (risk ratio 2.11, 95% confidence interval 1.37 to 3.2). However, this early difference was no longer present after this point in time. This suggests that the increased risk is limited to the early post-treatment period and that patients who had an event-free survival at 1 year have comparable clinical outcomes at 3 years.

Christiansen et al. (23) recently reported clinical outcomes among patients undergoing emergency PCI for AMI in patients with ULMCA ($n = 27$). Compared with our series, the population had similar baseline characteristics and a similar surgical risk score but did not receive DES routinely, and in 1 patient plain old balloon angioplasty alone was performed. The MACE rate at 6-month follow-up in Christiansen's report and in our group was 41% and 30%, respectively. Interestingly, CD was the most prominent component of MACE, consistent with our findings. In our series, the very-high-risk profile of patients in whom CD occurred (EuroSCORE 13 ± 3, mean EF 38 ± 11%, CS as diagnosis at admission in 8 of 15 patients) and absence of procedure-related or ST-related CDs suggest that CD occurred owing to the clinical presentation and comorbidities rather than the procedure or "performance" of the device implanted.

Comparison with CABG. Current ACC/AHA guidelines for PCI recommend surgical revascularization as the primary procedure for patients with ULMCA disease (6). The main reason for this recommendation is that long-term outcomes of surgical revascularization, including in the subpopulation with ULMCA disease, are available (24,25,26), whereas few data exist to allow evaluation of long-term safety and efficacy of PCI with DES for ULMCA disease, and no randomized trial has been published that compares the 2 treatments. Results of the ongoing SYNTAX (SYNergy Between PCI With TAXUS and Cardiac Surgery) and COMBAT (Comparison of Bypass Surgery and Angioplasty Using Sirolimus-Eluting Stents in Patients With Unprotected Left Main Coronary Artery Disease) studies are awaited.

Three-year cumulative survival of elective patients with ULMCA disease enrolled in the CASS (Collaborative Study in Coronary Artery Surgery) study was 91% for the surgical group (24), which is in line with the cumulative survival rate in our elective group (93.4%).

Recent retrospective studies (27,28) reported 1-year follow-up outcomes of patients undergoing CABG for ULMCA disease. The range of incidence of death, MI, TVR, and MACE was 5.2% to 8.5%, 15% to 32.4%, 5.5% to 5.7%, and 24.8% to 46.6%, respectively. Compared with our population, this represents a similar incidence of death and lower incidence of TVR but an apparently higher incidence of MI and MACE. In these studies, the average risk score and the proportion of patients stratified as at low- or high-risk scores are similar to the population in our study. However, because the assessment was performed with different risk score systems, caution should be taken while interpreting and comparing the outcomes of the aforementioned studies. The 3-year follow-up outcomes of CABG in elective patients with isolated ULMCA disease were recently described by d'Allonnes et al. (25). At 3 years, cumulative survival and freedom from MACE were 92% and 87%, respectively. Compared with our series, survival was comparable but our incidence of MACE was higher, mainly owing to the higher rate of TVR.

Stent thrombosis. In this registry, the definite ST occurred only in 2 cases. The patient in whom definite acute ST occurred was taking dual antiplatelet therapy, whereas the patient with very late ST was only taking aspirin at the time of the adverse event. Index PCI was performed in the context of acute coronary syndromes (unstable angina, emergent PCI) in the acute ST case, whereas in the other case the procedure was elective, performed in a patient with stable angina.

In our study, definite ST was not associated with CD, and the overall incidence was as low as in other high-risk DES populations. Real-world DES registries with long-term follow-up (15) have reported an overall incidence of

mortality related to ST of <10%, and most recently, in the ERACI (Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Multivessel Disease) III ST analysis (29), death related to "confirmed ST" occurred only in 1 of 5 patients (subacute ST in a patient who stopped clopidogrel 3 days before the event).

Conclusions

Very-long-term follow-up of patients with ULMCA disease treated with DES demonstrated a satisfactory rate in both single and composite outcomes. The progressive reduction of incidence of adverse events over time suggests that DES are persistently effective. Elective PCI patients had an excellent event-free survival over the 3-year period. The PCIs in emergent patients, although hampered by an early lower event-free survival, also had a favorable long-term clinical success rate. In terms of safety, the definite ST rate was lower than in other high-risk lesion subsets.

Reprint requests and correspondence: Dr. Patrick W. Serruys, Director of the Interventional Cardiology Department, Thoraxcenter, Erasmus Medical Center, Erasmus University, Dr. Molewaterplein 40, 3015 GD, Rotterdam, the Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl.

REFERENCES

1. Valgimigli M, van Mieghem CA, Ong AT, et al. Short- and long-term clinical outcome after drug-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: insights from the Rapamycin-Eluting and Taxus Stent Evaluated At Rotterdam Cardiology Hospital registries (RESEARCH and T-SEARCH). Circulation 2005;111:1383–9.
2. Valgimigli M, Malagutti P, Rodriguez Granillo GA, et al. Single-vessel versus bifurcation stenting for the treatment of distal left main coronary artery disease in the drug-eluting stenting era. Clinical and angiographic insights into the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) and Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registries. Am Heart J 2006;152:896–902.
3. Sheiban I, Meliga E, Moretti C, et al. Long-term clinical and angiographic outcomes of treatment of unprotected left main coronary artery stenosis with sirolimus-eluting stents. Am J Cardiol 2007;100: 431–5.
4. Chieffo A, Stankovic G, Bonizzoni E, et al. Early and mid-term results of drug-eluting stent implantation in unprotected left main. Circulation 2005;111:791–5.
5. Park SJ, Kim YH, Lee BK, et al. Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis: comparison with bare metal stent implantation. J Am Coll Cardiol 2005;45:351–6.
6. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). J Am Coll Cardiol 2004;44:e213–310.
7. Smith SC Jr., Feldman TE, Hirshfeld JW Jr., et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). J Am Coll Cardiol 2006;47:e1–121.
8. Webster MW, Ormiston JA. Drug-eluting stents and late stent thrombosis. Lancet 2007;370:914–5.
9. Park DW, Park SW, Lee SW, et al. Frequency of coronary arterial late angiographic stent thrombosis (LAST) in the first six months: outcomes with drug-eluting stents versus bare metal stents. Am J Cardiol 2007;99:774–8.
10. Jaffe R, Strauss BH. Late and very late thrombosis of drug-eluting stents: evolving concepts and perspectives. J Am Coll Cardiol 2007; 50:119–27.
11. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. J Am Coll Cardiol 2005;45:2088–92.
12. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol 2006;48:2584–91.
13. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16:9–13.
14. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
15. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.
16. Lee BK, Hong MK, Lee CW, et al. Five-year outcomes after stenting of unprotected left main coronary artery stenosis in patients with normal left ventricular function. Int J Cardiol 2007;115:208–13.
17. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
18. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
19. Schofer J, Schluter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet 2003;362:1093–9.
20. Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. Circulation 2003;107:38–42.
21. Morice MC, Colombo A, Meier B, et al. Sirolimus- vs paclitaxel-eluting stents in de novo coronary artery lesions: the REALITY trial: a randomized controlled trial. JAMA 2006;295:895–904.
22. Kastrati A, Dibra A, Mehilli J, et al. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. Circulation 2006;113:2293–300.
23. Christiansen EH, Lassen JF, Andersen HR, et al. Outcome of unprotected left main percutaneous coronary intervention in surgical low-risk, surgical high-risk, and acute myocardial infarction patients. Eurointervention 2006;1:403–8.
24. Caracciolo EA, Davis KB, Sopko G, et al. Comparison of surgical and medical group survival in patients with left main coronary artery disease. Long-term CASS experience. Circulation 1995;91:2325–34.
25. d'Allonnes FR, Corbineau H, Le Breton H, Leclercq C, Leguerrier A, Daubert C. Isolated left main coronary artery stenosis: long term follow up in 106 patients after surgery. Heart 2002;87:544–8.
26. Rolle F, Christidès C, Comu E. Sténoses significatives du tronc commun de l'artère coronaire gauche. Arch Mal Coeur 1994;87:899–905.
27. Chieffo A, Morici N, Maisano F, et al. Percutaneous treatment with drug-eluting stent implantation versus bypass surgery for unprotected left main stenosis: a single-center experience. Circulation 2006;113:2542–7.
28. Lee MS, Kapoor N, Jamal F, et al. Comparison of coronary artery bypass surgery with percutaneous coronary intervention with drug-eluting stents for unprotected left main coronary artery disease. J Am Coll Cardiol 2006;47:864–70.
29. Rodriguez AE, Mieres J, Fernandez-Pereira C, et al. Coronary stent thrombosis in the current drug-eluting stent era: insights from the ERACI III trial. J Am Coll Cardiol 2006;47:205–7.

APPENDIX

For supplementary tables, please see the online version of this article.

CHAPTER 3

IMPACT OF DRUG-ELUTING STENT SELECTION ON LONG-TERM CLINICAL OUTCOMES IN PATIENTS TREATED FOR UNPROTECTED LEFT MAIN CORONARY ARTERY DISEASE: THE SIROLIMUS VS PACLITAXEL DRUG-ELUTING STENT FOR LEFT MAIN REGISTRY (SP-DELFT)

Impact of drug-eluting stent selection on long-term clinical outcomes in patients treated for unprotected left main coronary artery disease: The sirolimus vs paclitaxel drug-eluting stent for left main registry (SP-DELFT)

E. Meliga [a,b], H.M. Garcia-Garcia [a], M. Valgimigli [c], A. Chieffo [d], G. Biondi-Zoccai [e], A.O. Maree [f], N. Gonzalo [a], S. Cook [g], S. Marra [b], C. Moretti [e], S. De Servi [h], I.F. Palacios [f], S. Windecker [g], R. van Domburg [a], A. Colombo [d], I. Sheiban [e], P.W. Serruys [a,*]

[a] *Department of Interventional Cardiology, Erasmus Medical Centre, Erasmus University, Rotterdam, The Netherlands*
[b] *Department of Interventional Cardiology, S. Giovanni Battista Hospital, Turin, Italy*
[c] *Department of Interventional Cardiology, S. Anna hospital, University of Ferrara, Ferrara, Italy*
[d] *Department of Interventional Cardiology, S. Raffaele Hospital, Milan, Italy*
[e] *University Department of Interventional Cardiology, S. Giovanni Battista Hospital, University of Turin, Turin, Italy*
[f] *Department of Interventional Cardiology, Massachusetts General Hospital, Boston, Massachusetts, USA*
[g] *Department of Interventional Cardiology, University Hospital, Bern, Switzerland*
[h] *Department of Cardiovascular Diseases, Ospedale Civile di Legnano, Legnano, Milan, Italy*

Received 19 March 2008; received in revised form 7 May 2008; accepted 1 June 2008

Abstract

Aim: To compare the long-term relative efficacy and safety of SES and PES in patients undergoing percutaneous coronary intervention (PCI) for unprotected left main coronary artery (ULMCA) disease and to evaluate the role of lesion location and stenting technique in determining outcomes.
Methods and results: From April 2002 to April 2004, 288 consecutive patients who underwent elective PCI with DES implantation for de novo lesions on ULMCA have been retrospectively selected and analyzed in seven European and US tertiary care centers. All patients had a minimum follow-up of 3 years. SES was used in 152 patients while 136 received PES. Isolated ostial–shaft disease was present in 27% of patients. Distal LM disease (73%) was treated with single and double stent approach in 29.5% and 43.4% of patients respectively. After 3 years, rates of survival free from any of the events investigated, were independent from lesion location and stenting approach and did not differ significantly between SES and PES groups. Freedom from MACE (SES vs. PES) was 76.3% vs. 83.1% in the ostial/shaft group, 80.3% vs. 72.8% in the distal-single stent group and 67.1% vs. 66.2% in the distal-double stent group. Definite stent thrombosis occurred only in 1(0.3%) patient at 439 days.
Conclusions: In elective patients who underwent PCI for de novo lesions in the ostium, shaft or distal ULMCA, long-term clinical outcomes with SES and PES use were similar independently of lesion location and stenting technique.

Keywords: Percutaneous coronary intervention; Unprotected left main coronary artery disease; Sirolimus eluting stent; Paclitaxel eluting stent

* Corresponding author. Interventional Cardiology Department, Thoraxcenter, Erasmus MC, Erasmus University, Dr Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands. Tel.: +31 104635260.
E-mail address: p.w.j.c.serruys@erasmusmc.nl (P.W. Serruys).

0167-5273/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ijcard.2008.06.006

Please cite this article as: Meliga E, et al, Impact of drug-eluting stent selection on long-term clinical outcomes in patients treated for unprotected left main coronary artery disease: The sirolimus vs paclitaxel drug-eluting stent for left main registry (SP-DELFT), Int J Cardiol (2008), doi:10.1016/j.ijcard.2008.06.006

1. Introduction

Percutaneous coronary intervention (PCI) using drug-eluting stents (DES) has become the preferred revascularization strategy for unprotected left main coronary artery (ULMCA) disease in patients at high risk for surgery. Recent studies report encouraging long-term clinical outcome [1–4]. However, lesion location and stenting technique can influence the incidence of adverse events. Presence of ostial and shaft lesions is associated with favorable outcome and a low restenosis rate [5,6]. In contrast, revascularization of distal LMCA lesions is associated with less favorable outcome, particularly when a double stent approach is preferred [7].

The 2 most widely used and studied drug-eluting stents are the sirolimus-eluting stent (SES; Cypher, Johnson & Johnson Cordis, Miami, Florida) and paclitaxel-eluting stent (PES; Taxus, Boston Scientific, Natick, Massachusetts). Recent studies evaluating the relative safety and efficacy of both DESs in a variety of patient subsets have shown inconsistent results [8,9]. Importantly, there is little data comparing clinical outcome associated with use of SES and PES to treat ULMCA disease, and studies reporting very long-term data are notably lacking. Thus, the aim of this study was to compare the relative efficacy and safety of PCI with SES and PES in patients with ULMCA disease. In addition, the role of lesion location and stenting technique in determining outcome was evaluated.

2. Methods

2.1. Population

Consecutive patients who underwent elective PCI with SES or PES for de novo lesions in the ostium, shaft or distal ULMCA between April 2002 and April 2004 in seven European and US tertiary health care centers, were identified retrospectively and analyzed. Patients with acute myocardial infarctions or cardiogenic shock were excluded from the analysis. All patients had confirmed myocardial ischemia related to ULMCA disease. Factors that determined choice of a percutaneous approach over surgery included coronary anatomy and lesion characteristics, patient preference, referring physician preference and surgical risk. High surgical risk was defined as a EuroSCORE (European system for cardiac operative risk evaluation) >6. All patients provided written informed consent prior to the procedure. Data analysis was performed with the approval of the institutional ethics committees of the hospitals and/or universities involved.

2.2. Procedures and medications

All PCIs were performed according to concurrent guidelines. Type of stent, stenting strategy, use of periprocedural glycoprotein IIb/IIIa inhibitors, route of arterial access, predilation devices, intravascular ultrasound guidance and prophylactic intra-aortic balloon pump use was at the discretion of the operator. The choice to use a single or double stent strategy was driven by the anatomical location and extent of coronary artery disease. In general, a single stent strategy was used in isolated distal ULMCA stenosis (DISTAL-Single) and a double stent strategy in cases of distal ULMCA stenosis involving both left anterior descending (LAD) and left circumflex (LCX) coronary artery ostia (DISTAL-Double) or in cases where plaque shift occurred. All patients were pretreated with aspirin, clopidogrel (75 mg/day 3 days prior to the procedure or 300-mg loading dose) and low-molecular-weight or unfractioned heparin (administered in the cath-lab, before guide-wire insertion). Heparin was titrated to maintain an activated clotting time >250 s. After the procedure, all patients were prescribed lifelong aspirin (75–100 mg/day) and prolonged (at least six months) dual antiplatelet therapy (DAT) of aspirin 100 mg/day and 75 mg/day clopidogrel or 250 mg ticlopidine twice daily. Repeated revascularization was only performed if there was either symptom recurrence or inducible ischemia related to the ULMCA disease.

2.3. Definitions

Technical success was defined as successful deployment of a stent(s) in the target lesion. *Procedural success* was defined as ULMCA revascularization with ≤30% residual diameter stenosis by quantitative coronary angiography, without major procedural or post-procedural adverse events (death, myocardial infarction, emergency target vessel revascularization or acute stent thrombosis). *Death* was classified as either cardiac (CD) or non-cardiac, according to the Academic Research Consortium (ARC) definition. Deaths that could not be classified were considered cardiac. *Target lesion revascularization* (TLR) was defined as any repeat percutaneous intervention of the target lesion or other complication of the target lesion. The target lesion was defined as the treated segment from 5 mm proximal to the stent to 5 mm distal to the stent. *Target vessel revascularization* (TVR) was defined as any repeat PCI of any segment of the target vessel, defined as the entire major coronary vessel proximal and distal to the target lesion, including upstream and downstream branches and the target lesion itself. *Major adverse cardiac event* (MACE) was defined as the occurrence of cardiac death (CD), nonfatal myocardial infarction (MI) or TVR during the follow-up period.

Definite, probable and possible stent thromboses (ST) were determined according to the ARC definitions. Stent thrombosis was defined as acute, sub-acute, late and very late if the event occurred within 24 h, 30 days, <1 year or >1 year respectively, after the procedure. *Myocardial infarction* was defined as creatine kinase-MB mass increase >3 times the upper limit of normal, associated with chest pain lasting >30 min or with new evident electrocardiographic changes.

2.4. Data collection, and follow-up

All data relating to hospital admissions, procedures and in-hospital outcomes were collected in each center using the hospital recording network. Clinical follow-up was scheduled

Please cite this article as: Meliga E, et al, Impact of drug-eluting stent selection on long-term clinical outcomes in patients treated for unprotected left main coronary artery disease: The sirolimus vs paclitaxel drug-eluting stent for left main registry (SP-DELFT), Int J Cardiol (2008), doi:10.1016/j.ijcard.2008.06.006

for all patients every 6 months up to 48 months by office visit or telephone interview. When the patient was not reachable, the information was sought from the referring physician, hospital electronic database or Municipal Civil Registries. At 3 years the clinical follow-up was 100%. This protocol was approved by the hospital ethics committees and is in accordance with the Declaration of Helsinki.

2.5. Statistical analysis

Normally distributed variables were analyzed using parametric tests and non-normally distributed data using non-parametric tests. Continuous variables are expressed as mean±SD or median±SD and differences were compared using Student *t* test or Mann Whitney test. Categorical variables are expressed as counts and percentages. Differences between sub-groups were assessed by Fisher exact test or chi-square test, as appropriate. Differences between the SES and PES groups were also tested according to lesion location. MACEs were reported hierarchically. A propensity score was constructed using logistic regression to control for potential confounders. The propensity score addressed the probability that a patient would receive either a SES or a PES and was computed using a logistic regression model, into which all the baseline clinical and angiographic variables contained in Tables 1 and 2 were entered. To adjust for possible confounders between the two groups, the resulting score as well as clinical, angiographic and procedural variables with a p value <0.1, were included as covariates in a Cox proportional hazards regression model. Survival curves were generated at mean of covariates and differences between groups were evaluated and reported using hazard ratios (HRs) with 95% CI and p values. Landmark analysis was performed with the landmark set at 12 months to provide separate descriptions of the early and late relative risk of MACE in the SES and PES sub-groups. Outcomes between the two sub-groups were compared using risk ratios with 95% CIs. All analyses were performed using SPSS version 12 statistical software (SPSS Inc., Chicago, Illinois). A two-tailed p value <0.05 was considered significant for hypothesis testing.

Table 1
Baseline clinical characteristics, *n* (%)

	SES (n=152)	PES (n=136)	P value
Age	65.7±11.3	65.6±11.1	0.94
Men	110 (72.3)	103 (75.7)	0.59
BMI	27.4±4.1	26.5±5.4	0.34
Arterial hypertension	107 (70.3)	85 (62.5)	0.16
Hypercholesterolemia	100 (65.7)	88 (64.7)	0.8
Current smoking	52 (34.2)	46 (33.8)	0.99
Diabetics	55 (36.1)	39 (28.6)	0.16
IDDM	24 (15.8)	28 (20.5)	0.35
Familiar risk factor	35 (23)	38 (27.9)	0.34
Previous AMI	72 (47.3)	66 (48.5)	0.9
Previous PCI	53 (34.8)	44 (32.3)	0.7
Previous CABG	41 (27)	35 (25.7)	0.89
Diagnosis at admission			
Stable angina	72 (47.3)	86 (63.2)	0.006
Unstable angina	75 (49.3)	46 (33.8)	0.007
Silent ischemia	5 (3.2)	4 (2.9)	0.86
LVEF	49.4±12.3	50±11.7	0.7
EuroSCORE	6.1±4	5.3±3.5	0.07

BMI, body mass index; IDDM, insulin dependent diabetes mellitus; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery by-pass graft;, LVEF, left ventricular ejection fraction.

Table 2
Angiographic and procedural characteristics, *n* (%)

	SES (n=152)	PES (n=136)	P value
Ostium/shaft lesions	37 (24.3)	41 (30.1)	0.26
Distal lesions	115 (75.6)	95 (69.8)	0.29
Single stent approach	48 (31.5)	37 (27.2)	0.41
Multiple stent approach	67 (44)	58 (42.6)	0.9
V stenting	13 (8.5)	9 (6.6)	0.53
T stenting	19 (12.5)	2 (1.4)	<0.001
Crushing	35 (23)	24 (17.6)	0.25
Culotte	0 (0)	23 (16.9)	<0.001
Stents per patient	1.5	1.46	0.59
Stent diameter	3.18±0.32	3.31±0.29	<0.001
Stent length	17±7.5	18.6±6.9	0.07
Pre-dilation	72 (47.3)	51 (37.5)	0.19
Thrombectomy	2 (1.3)	0 (0)	0.5
Cutting	13 (8.5)	14 (10.2)	0.68
Rotablator	3 (1.9)	4 (2.9)	0.71
Atherectomy	2 (1.3)	3 (2.2)	0.67
Post-dilation	89 (58.5)	59 (43.3)	0.005
Post procedural RVD	3.71±0.64	3.74±0.46	0.79
Post procedural MLD	3.33±0.65	3.31±0.52	0.86
Other vessels treated	75 (49.3)	67 (49.2)	0.99

DES, drug-eluting stent; RVD, reference vessel diameter; MLD, minimal lumen diameter; FU, follow-up.

Table 3
Adjusted freedom from CD, MI, TLR, TVR and MACE (%) at 3-years FU in the ostial/shaft, distal-single stent and distal-multi stent groups

	SES (n=152)	PES (n=136)	HRs	95% CI	P value
Ostial/shaft (n=78)					
CD	98.7	99.3	1.27	0.56–2.8	0.62
MI	93.8	96.7	3.57	0.36–8.9	0.27
TLR	96.1	96.3	1.03	0.06–1.41	0.86
TVR	94.1	85.3	0.4	0.63–2.58	0.33
MACE	76.3	83.1	1.78	0.53–5.94	0.34
Distal-single (n=85)					
CD	96.7	92.6	0.51	0.09–2.67	0.42
MI	99.3	96.3	0.2	0.02–1.82	0.15
TLR	98.7	98.5	0.72	0.15–4.8	0.81
TVR	93.4	84.6	0.45	0.11–1.7	0.24
MACE	80.3	72.8	0.5	0.2–1.27	0.14
Distal-double (n=125)					
CD	97.4	95.6	0.46	0.1–2.2	0.34
MI	90.1	86.8	0.76	0.25–2.3	0.63
TLR	89.5	85.3	0.56	0.15–2.1	0.39
TVR	86.2	83.8	0.54	0.17–1.67	0.28
MACE	67.1	66.2	0.61	0.3–1.21	0.15

CD, cardiac death; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; MACE, major adverse cardiovascular events.

Please cite this article as: Meliga E, et al, Impact of drug-eluting stent selection on long-term clinical outcomes in patients treated for unprotected left main coronary artery disease: The sirolimus vs paclitaxel drug-eluting stent for left main registry (SP-DELFT), Int J Cardiol (2008), doi:10.1016/j.ijcard.2008.06.006

3. Results

3.1. Baseline clinical, angiographic and procedural characteristics

Baseline clinical, angiographic and procedural characteristics of all patients (n=288) stratified by DES type are shown in Tables 1 and 2. During the same period, a total of 680 patients with significant ULMCA disease underwent CABG in the 7 participating centers. The SES group (n=152 patients) and PES group (n=136 patients) were comparable in all baseline characteristics with the exception of clinical presentation, the use of T and culotte stenting techniques, mean stent diameter and use of post-dilatation. In both groups, approximately 75% of all lesions were distal and 60% of these were treated with a double stent approach. The favored stenting technique was crush stenting. Differences depending on lesion location were tested and were not significant.

3.2. Follow-up clinical outcomes

Clinical outcome at 3 years is stratified by DES type, lesion location and stenting approach and shown in Table 3. All patients were followed-up for at least 36 months (range: from 36 to 60.2). Rates of survival free from any of the events investigated were independent from lesion location and stenting approach and did not differ significantly between SES and PES groups. In the DISTAL-double subgroup, use of T-stenting technique was associated with a significantly lower incidence of MACE (HR 0.21, 95% CI: 0.05–0.97, p=0.046). Adjusted curves derived from Cox survival analysis are displayed in Fig. 1. Freedom from MACE (SES vs. PES) was 76.3% and 83.1% in the ostial/shaft group, 80.3% and 72.8% in the DISTAL-single group and 67.1% vs. 66.2% in the DISTAL-double group.

After pooling the DISTAL-single and DISTAL-double sub-groups, 3-year freedom from MACE in the SES and PES groups was 75.4% and 67.3% respectively (HR 0.65, 95% CI 0.37–1.15, p=0.15).

Definite ST occurred in 1 (0.3%) patients at 439 days (very late ST). Probable ST occurred in 1 (0.3%) patient and possible ST in 12 (4.2%) patients. No acute, sub-acute and late ST occurred. Very late ST occurred in a patient with stable angina who underwent an elective PCI and received 3 PES for a significant lesion located in the distal left main (LM). One-year DAT was recommended and, thus, at the time of the ST event

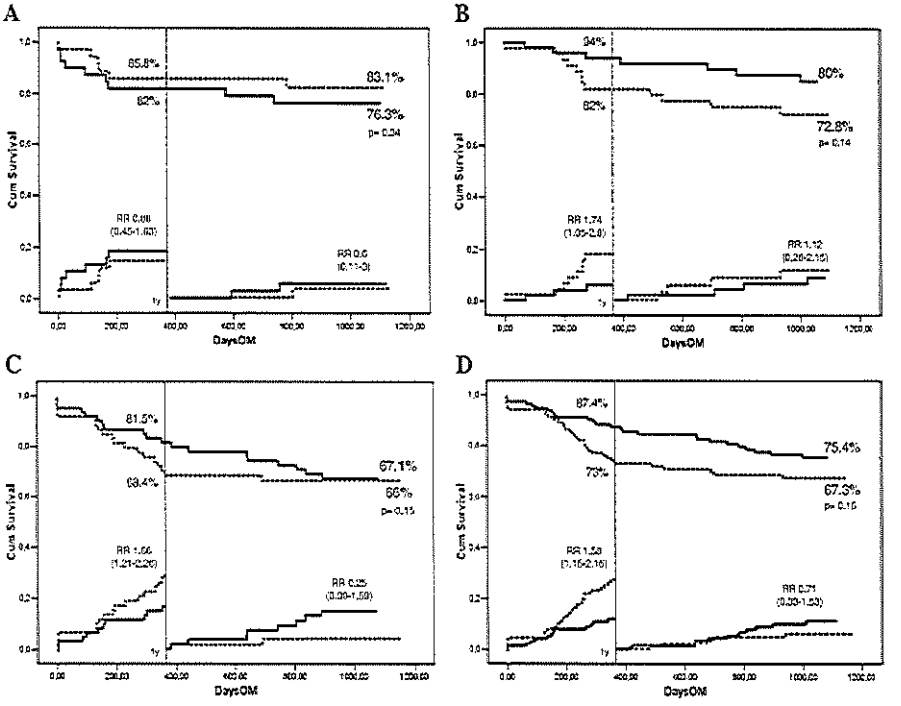


Fig. 1. Adjusted MACE-free survival curves and landmark analysis of the ostial/shaft (panel A), DISTAL-single (panel B), DISTAL-double (panel C) and whole DISTAL (panel D) groups. Solid lines, SES group; dotted lines, PES group; RR, PES-SES risk ratio with 95% confidence interval (in brackets). DaysOM, Days free from MACE. Landmark was positioned at 1 year (1y).

Please cite this article as: Meliga E, et al. Impact of drug-eluting stent selection on long-term clinical outcomes in patients treated for unprotected left main coronary artery disease: The sirolimus vs paclitaxel drug-eluting stent for left main registry (SP-DELFT). Int J Cardiol (2008), doi:10.1016/j.ijcard.2008.06.006

was not ongoing. The event occurred in a patient who was classified as very high-risk patient (euroSCORE = 11). The ST event did not result in CD.

4. Discussion

The main findings of this study are the following: 1) at 3 years, patients treated with SES and PES had similar incidence of CD, MI, TLR, TVR and MACE-free survival; 2) SES and PES performed comparably in bifurcation lesions, independent of whether a single and double stent approach was employed; 3) the majority of events in either group occurred within the first year, suggesting that the safety and efficacy profile of the two stents remain unchanged at long-term follow-up; 4) when compared to SES, PES was associated with a higher incidence of MACE only within the first year of follow-up.

Since their introduction into clinical practice, a number of trials and meta-analyses have compared efficacy and safety of SES and PES. In some cases, the results indicated that SES use was associated with a lower risk of MACE [10], re-intervention and stent thrombosis [9] while other studies demonstrated no differences in outcome [8,11]. In addition, others indicate that SES use may be associated with a lower incidence of TLR when deployed in challenging/high-risk lesions such as bifurcation lesions [12], small vessel size lesions [13] and long lesions [14].

Data comparing the relative safety and efficacy of SES and PES in patients with ULMCA disease are lacking and when available only provide short-mid term follow-up. A previous study [15] reported no significant difference in angiographic and clinical outcomes associated with SES and PES use for LMCA PCI at a median follow-up of 22 months. However, long-term data are not available and it is still unclear whether lesion location or complexity may have a differential affect on device performance and result in a significant difference in clinical outcomes. This has been shown in non-ULMCA populations.

In our overall study cohort, adjusted freedom from adverse events at 3-year follow-up did not differ significantly between the SES and PES groups. The presumed advantage of SES in terms of TLR and MACE was not confirmed in this series of patients. Our findings indicate that performance of the two stents varies over time but that 3 year outcome does not differ significantly.

In patients with ostial/shaft lesions of an ULMCA, both SES and PES were associated with excellent long-term clinical outcome. Our results were in line with those recently reported by Chieffo et al. in a similar population [5]. Interestingly, in our study freedom from CD (98.7% SES vs. 99.3% PES, $p = 0.62$), TLR (96.1% SES vs. 96.3% PES $p = 0.86$) and MACE (76.3% SES vs. 83.1% PES, $p = 0.34$) was comparable to that reported in studies of highly selected populations with single de novo lesions that excluded patients with ULMCA disease [16,17] Thus percutaneous treatment for this type of lesion may have the safety and efficacy requirements to be considered primary therapy.

In most non-left main randomized controlled trials, the lower incidence of TLR for SES was mainly related to a significantly lower in-stent late loss compared to PES. The impact of late lumen loss on vessel haemodynamics in ostial left main lesions may be less significant due to the relatively short stent length and bigger stent diameter. Thus, clinical outcome may depend less on differences between the two devices. Landmark analysis of the ostial/shaft sub-group showed that the two stents behaved similarly over time. Most adverse events in either both groups occurred within the first year (75% SES vs 82% PES). Thereafter the survival curves flattened progressively, suggesting a persistent anti-proliferative effect of DES through time.

Analysis of lesions involving the distal portion of ULMCA revealed no significant difference between SES and PES in the incidence of CD, MI, TLR, TVR and MACE at 3-years. The stents performed equally whether the lesion was treated with a single or double stent approach. A previous study [12] with shorter follow-up reported that the deformed stent structure and overlapped struts may alter drug distribution and reduce the efficacy of PES under these conditions, however this finding was not replicated in our study. In fact, in both the DISTAL-single and DISTAL-double sub-groups, the landmark analysis showed a significantly higher risk ratio in terms of MACE associated with use of PES within the first year that was not confirmed at the end of the follow-up period.

Effects of sample size on these results and the possibility of introducing a type II error were tested by pooling the two DISTAL sub-groups. In this setting the landmark analysis again showed a significantly higher incidence of MACE associated with use of PES only within the first year. In line with these results, long-term follow-up IVUS studies conducted in patients treated with SES [18] and PES [19] show that, after the 1st year, the increase of neointimal volume was still significant in the SES (84% increase between 1st and 2nd year and an additional 37% increase between the 2nd and the 4th) while it held almost steady in the PES (<5% increase after the 1st year), suggesting a possible "catch-up" phenomenon over time with SES. It is interesting to note that, in the DISTAL-double sub-group, the use of T-stenting technique was significantly associated with a lower incidence of MACE (HR 0.21, 95% CI: 0.04–0.97, $p = 0.04$), suggesting that a less "aggressive" approach, when feasible, lead to better clinical outcomes independent of DES type implanted.

In this registry, definite ST occurred only in 1 case. The patient in whom definite ST occurred received 3 PES and was only taking aspirin at the time of the adverse event. In our study, definite ST was not associated with cardiac death and the overall incidence was as low as in other high-risk DES populations.

4.1. Limitations

The present study was designed as a retrospective multicenter registry and therefore lacks randomization and intention-to-treat data. Significant differences between the two sub-

Please cite this article as: Meliga E, et al, Impact of drug-eluting stent selection on long-term clinical outcomes in patients treated for unprotected left main coronary artery disease: The sirolimus vs paclitaxel drug-eluting stent for left main registry (SP-DELFT), Int J Cardiol (2008), doi:10.1016/j.ijcard.2008.06.006

groups in terms of stent diameter, stenting technique and use of post-dilation, though included in the Cox model, may have influenced the results. Moreover, since no sample size calculations were performed, we acknowledge that our results may be affected by a type II error.

5. Conclusions

In elective patients who underwent PCI for de novo lesions in the ostium, shaft or distal ULMCA, long-term clinical outcomes with SES and PES use were similar and this finding was independent of lesion location and stenting technique. The proposed advantage of SES, reported in some non-left main trials, was not confirmed in the present study. Our long-term clinical data suggest that in ULMCA lesions, SES and PES perform differently over time but ultimately are associated with similar clinical outcome.

References

[1] Valgimigli M, van Mieghem CA, Ong AT, Aoki J, et al. Short- and long-term clinical outcome after drug-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: insights from the Rapamycin-Eluting and Taxus Stent Evaluated at Rotterdam Cardiology Hospital registries (RESEARCH and T-SEARCH). Circulation 2005;111(11):1383–9.

[2] Valgimigli M, Malagutti P, Rodriguez Granillo GA, et al. Single-vessel versus bifurcation stenting for the treatment of distal left main coronary artery disease in the drug-eluting stenting era. Clinical and angiographic insights into the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) and Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registries. Am Heart J 2006;152(5):896–902.

[3] Sheiban I, Meliga E, Moretti C, et al. Long-term clinical and angiographic outcomes of treatment of unprotected left main coronary artery stenosis with sirolimus-eluting stents. Am J Cardiol 2007;100(3):431–5.

[4] Park SJ, Kim YH, Lee BK, et al. Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis: comparison with bare metal stent implantation. J Am Coll Cardiol 2005;45(3):351–6.

[5] Chieffo A, Park SJ, Valgimigli M, et al. Favorable long-term outcome after drug-eluting stent implantation in nonbifurcation lesions that involve unprotected left main coronary artery: a multicenter registry. Circulation 2007;116(2):158–62.

[6] Valgimigli M, Malagutti P, Rodriguez-Granillo GA, et al. Distal left main coronary disease is a major predictor of outcome in patients undergoing percutaneous intervention in the drug-eluting stent era: an integrated clinical and angiographic analysis based on the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) and Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registries. J Am Coll Cardiol 2006;47(8):1530–7.

[7] Baim DS, Mauri L, Cutlip DC. Drug-eluting stenting for unprotected left main coronary artery disease: are we ready to replace bypass surgery? J Am Coll Cardiol 2006;47(4):878–81.

[8] Kereiakes DJ. The Emperor's new clothes: another cypher versus taxus post-hoc meta-analysis. J Am Coll Cardiol 2007;50(14):1381–5.

[9] Schomig A, Dibra A, Windecker S, et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. J Am Coll Cardiol 2007;50(14):1373–80.

[10] Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353(7):653–62.

[11] Morice MC, Colombo A, Meier B, et al. Sirolimus- vs paclitaxel-eluting stents in de novo coronary artery lesions: the REALITY trial: a randomized controlled trial. Jama 2006;295(8):895–904.

[12] Pan M, Suarez de Lezo J, Medina A, et al. Drug-eluting stents for the treatment of bifurcation lesions: a randomized comparison between paclitaxel and sirolimus stents. Am Heart J 2007;153(1):15 e11–17.

[13] Togni M, Eber S, Widmer J, et al. Impact of vessel size on outcome after implantation of sirolimus-eluting and paclitaxel-eluting stents: a subgroup analysis of the SIRTAX trial. J Am Coll Cardiol 2007;50(12):1123–31.

[14] Kim YH, Park SW, Lee SW, et al. Sirolimus-eluting stent versus paclitaxel-eluting stent for patients with long coronary artery disease. Circulation 2006;114(20):2148–53.

[15] Valgimigli M, Malagutti P, Aoki J, et al. Sirolimus-eluting versus paclitaxel-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: a combined RESEARCH and T-SEARCH long-term analysis. J Am Coll Cardiol 2006;47(3):507–14.

[16] Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349(14):1315–23.

[17] Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350(3):221–31.

[18] Aoki J, Abiznid AC, Serruys PW, et al. Evaluation of four-year coronary artery response after sirolimus-eluting stent implantation using serial quantitative intravascular ultrasound and computer-assisted grayscale value analysis for plaque composition in event-free patients. J Am Coll Cardiol 2005;46(9):1670–6.

[19] Tsuchida K, Serruys PW, Bruining N, et al. Two-year serial coronary angiographic and intravascular ultrasound analysis of in-stent angiographic late lumen loss and ultrasonic neointimal volume from the TAXUS II trial. Am J Cardiol 2007;99(5):607–15.

Please cite this article as: Meliga E, et al, Impact of drug-eluting stent selection on long-term clinical outcomes in patients treated for unprotected left main coronary artery disease: The sirolimus vs paclitaxel drug-eluting stent for left main registry (SP-DELFT), Int J Cardiol (2008), doi:10.1016/j.ijcard.2008.06.006

CHAPTER 4

DIABETIC PATIENTS TREATED FOR UNPROTECTED LEFT MAIN CORONARY ARTERY DISEASE WITH DRUG ELUTING STENTS: A 3-YEAR CLINICAL OUTCOME STUDY. THE DIABETES AND DRUG ELUTING STENT FOR LEFT MAIN REGISTRY (D-DELFT)

EuroIntervention

Diabetic patients treated for unprotected left main coronary artery disease with drug eluting stents: a 3-year clinical outcome study. The Diabetes and Drug Eluting stent for LeFT main registry (D-DELFT)

Emanuele Meliga[1,2], MD; Hector M Garcia-Garcia[1], MD, MSc; Marco Valgimigli[3], MD, PhD; Alaide Chieffo[4], MD; Giuseppe Biondi-Zoccai[5], MD; Andrew O Maree[6], MD; Nieves Gonzalo[1], MD; Stephane Cook[7], MD; Ignacio Cruz-Gonzalez[6], MD; Sebastiano Marra[2], MD; Stefano De Servi[8], MD; Igor F Palacios[6], MD; Stephan Windecker[7], MD; Ron van Domburg[1], PhD; Antonio Colombo[4], MD; Imad Sheiban[5], MD; Patrick W Serruys[1], MD, PhD, FACC, FESC.

1. Department of Interventional Cardiology, Erasmus Medical Centre, Erasmus University, Rotterdam, The Netherlands; 2. Department of Interventional Cardiology, S. Giovanni Battista Hospital, Turin, Italy; 3. Department of Interventional Cardiology, S. Anna hospital, University of Ferrara, Ferrara, Italy; 4. Department of Interventional Cardiology, S.Raffaele Hospital, Milan, Italy; 5. University Department of Interventional Cardiology, S. Giovanni Battista Hospital, University of Turin, Turin, Italy; 6. Department of Interventional Cardiology, Massachusetts General Hospital, Boston, Massachusetts, USA; 7. Department of Interventional Cardiology, University Hospital, Bern, Switzerland; 8. Department of Cardiovascular Diseases, Ospedale Civile di Legnano, Legnano (Milan) Italy

None of the authors have a conflict of interest to declare.

KEYWORDS
Diabetes mellitus, unprotected left main coronary artery disease, drug eluting stents

Abstract

Aims: Diabetes mellitus (DM) plays an important role in the development of coronary artery disease. Although previous studies have associated drug-eluting stent (DES) implantation in diabetic patients with favourable clinical and angiographic outcomes, the very long-term efficacy of these devices in diabetic patients undergoing PCI for significant unprotected left main coronary artery (ULMCA) disease has not been established yet.

Methods and results: Consecutive diabetic patients (n=100), who underwent elective PCI with DES for *de novo* lesions in an ULMCA between April 2002 and April 2004 in seven tertiary health care centres, were identified retrospectively and analysed. Consecutive non-diabetic patients (n=193), who underwent elective DES implantation for unprotected ULMCA disease, were selected as a control group. All patients were followed for at least 36 months. At 3-years follow-up, freedom from cardiac death & myocardial infarction (CDMI), target lesion revascularisation (TLR) and target vessel revascularisation (TVR) did not differ significantly between groups. The adjusted freedom from major adverse cardiac events (MACE, defined as the occurrence of CD, MI or TVR) was 63.4% in the DM group and 77.6% in the controls ($p<0.001$). When divided into IDDM and NIDDM sub-groups, insulin-dependent DM (IDDM) but not non IDDM (NIDDM) patients had significantly lower freedom from CDMI, TLR, TVR and MACE compared to controls.

Conclusions: These results suggest that major improvements in DES technology and pharmacotherapy are still required to improve clinical outcome and that the decision to perform percutaneous revascularisation in this subset of patients should be taken cautiously and on a case by case basis.

* *Corresponding author: Thoraxcenter, Ba-583, 's Gravendijkwal 240, 3015 CE, Rotterdam, The Netherlands*
E-mail: p.w.j.c.serruys@erasmusmc.nl

Introduction

Diabetes mellitus negatively impacts clinical outcome in patients undergoing surgical or percutaneous arterial revascularisation[1-3]. Proposed explanations for this increased vulnerability include greater atherosclerotic plaque burden, longer lesion length and aberrant neointimal proliferation after stenting in diabetics. Several trials conducted in diabetic patients determined that percutaneous coronary intervention (PCI) with drug-eluting stents (DES) significantly reduced restenosis, resulting in superior long-term clinical and angiographic results, when compared with bare metal stents (BMS)[4,5]. However, whether PCI with DES is a safe and effective alternative to CABG remains a matter of debate[6-9]. Importantly, there is little data that addresses clinical outcome associated with DES use to treat unprotected left main coronary artery (ULMCA) disease in diabetic patients, and studies reporting very-long term data are notably lacking.

Thus, the aim of this study was to report for the first time, very-long term clinical outcome data for diabetic patients undergoing PCI to ULMCA lesions with DES, and to identify potential predictors of adverse events using an international, multicentre, retrospective registry design.

Methods

Population

Consecutive diabetic patients who underwent elective PCI with SES or PES for *de novo* lesions in an ULMCA between April 2002 and April 2004 in seven European and US tertiary health care centres, were identified retrospectively and analysed. Patients were eligible for inclusion if they were undergoing pharmacological treatment with either hypoglycaemic agents or insulin at the time of the index procedure. Patients with acute myocardial infarction or cardiogenic shock at the time of admission were excluded from the analysis. Consecutive non-diabetic patients, who underwent elective DES implantation for unprotected ULMCA disease at the same centres over the same time period, were selected as a control group. All patients had confirmed myocardial ischaemia related to ULMCA disease. Factors that determined choice of a percutaneous approach over surgery included coronary anatomy and lesion characteristics, patient preference, referring physician preference and surgical risk. Patients were stratified by risk class using the European System for Cardiac Operative Risk Evaluation (EuroSCORE) (Table 1). Subjects with a EuroSCORE >6 were defined as high-risk and those with a EuroSCORE >9 as very high-risk. Data analysis was performed with the approval of the institutional ethics committees of the hospitals and/or universities involved.

Procedures and medications

All PCIs were performed according to current guidelines. Route of arterial access, type of stent, stenting strategy, use of periprocedural glycoprotein IIb/IIIa inhibitors, intravascular ultrasound guidance and prophylactic intra-aortic balloon pump use was at the discretion of the operator.

Table 1. Baseline clinical characteristics.

	DM (n=100)	nonDM (n=193)	p value
Age (years)	66.5±9.6	65.4±11.8	0.44
Men	72(72)	141(73.1)	0.79
BMI (Kg/m^2)	27.7±4.7	26.4±5	0.18
Arterial hypertension	71(71)	124(64.2)	0.29
Hypercholesterolaemia	66(66)	127(65.8)	0.98
Current smoking	40(40)	59(30.6)	0.12
IDDM	56(56)	0(0)	NA
NIDDM	44(44)	0(0)	NA
Familiar risk factor	30(30)	44(22.8)	0.18
Previous AMI	53(53)	86(44.6)	0.18
Previous PCI	36(36)	62(32.1)	0.52
Previous CABG	19(19)	31(16)	0.52
Diagnosis at admission			
Stable angina	50(50)	107(55.4)	0.37
Unstable angina	49(49)	77(39.9)	0.13
Silent ischaemia	1(1)	9(4.7)	0.09
LVEF (%)	51.3±11.6	48.7±12.2	0.1
EuroScore	6.2±3.74	5.66±3.96	0.26

DM: diabetic patients; nonDM: non diabetic patients (control group); BMI: body mass index; IDDM: insulin-dependent diabetes mellitus; NIDDM: non insulin-dependent diabetes mellitus; AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; LVEF: left ventricular ejection fraction

All patients received 325mg of aspirin, clopidogrel (75 mg/day three days prior to the procedure or 300-mg loading dose) and low-molecular-weight or unfractioned heparin titrated to maintain an activated clotting time >250 s. Complete revascularisation was attempted in all patients at the time of the index PCI. Significant lesions that were not treated during the index procedure were staged and treated generally within one month. After the procedure, all patients were prescribed lifelong aspirin (75-100 mg/day) and prolonged (at least six months) dual antiplatelet therapy (DAT) of aspirin 100-325 mg/d and 75 mg/d clopidogrel or 250 mg ticlopidine twice daily. Repeat revascularisation was only performed if there was either symptom recurrence or inducible ischemia related to the ULMCA disease.

Definitions

Technical success was defined as successful deployment of a stent(s) in the target lesion.

Procedural success was defined as ULMCA revascularisation with ≤ 30% residual diameter stenosis by quantitative coronary angiography, without major procedural or post-procedural adverse events (death, myocardial infarction, emergency target vessel revascularisation or acute stent thrombosis).

Death was classified as either cardiac (CD) or non-cardiac, according to the Academic Research Consortium (ARC) definition[10]. Deaths that could not be classified were considered cardiac.

Target lesion revascularisation (TLR) was defined as any repeat percutaneous intervention of the target lesion performed for

restenosis or other complication of the target lesion. The target lesion was defined as the treated segment from 5 mm proximal to the stent to 5 mm distal to the stent.

Target vessel revascularisation (TVR) was defined as any repeat PCI of any segment of the target vessel, defined as the entire major coronary vessel proximal and distal to the target lesion, including upstream and downstream branches and the target lesion itself. In the context of LMCA disease, the TVR definition comprises the whole left coronary system.

Major adverse cardiac event (MACE) was defined as the occurrence of cardiac death (CD), nonfatal myocardial infarction (MI) or TVR during the follow-up period.

Definite, probable and possible stent thromboses were determined according to the ARC definitions. Stent thrombosis was defined as acute, sub-acute, late and very late if the event occurred within 24 hr, 30 days, <1 year or >1 year respectively, after the procedure. Myocardial infarction was defined as creatine kinase-MB mass increase >3 times the upper limit of normal, associated with chest pain lasting >30 min or with new evident electrocardiographic changes.

Data collection, and follow-up

Information regarding clinical status was collected at clinic visits and by telephone interview scheduled 30 days after the procedure and then every six months. When the patient was not reachable, information were gathered from the referring physician, hospital electronic database or Municipal Civil Registries. The data collection was carried out using a dedicated electronic case report form (CRF). All the explored variables in the CRF were defined and number-coded before the CRF was sent to each participating centre. At three years the clinical follow-up was 100%. This protocol was approved by the hospital ethics committees and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

Statistical analysis

Normally distributed variables were analysed using parametric tests and non-normally distributed data using non-parametric tests. Continuous variables are expressed as mean ±SD and differences were compared using Student *t* test. Categorical variables are expressed as counts and percentages. Differences between sub-groups were assessed by Fisher exact test or chi-square test, as appropriate. Bivariate and multiple variable analyses were performed to identify independent predictors of adverse events. Specifically, all variables significantly associated with the clinical event of interest on bivariate analysis ($p<0.10$) were entered into subsequent models. After appropriate checks for underlying assumptions, multivariate Cox proportional hazard analysis was then performed, with the enter method for all pertinent covariates. Results of multivariate Cox analyses are reported as hazard ratios (HR) with 95% confidence intervals and p values. MACEs were reported hierarchically. Survival curves were generated at mean of covariates and differences between groups were evaluated and reported using hazard ratios (HRs) with 95% CI and p values. Landmark analysis was performed with the landmark set at 12 months to provide separate descriptions of the early and late relative risk of MACE in the SES and PES sub-groups. Outcomes in the two sub-groups were compared using risk ratios with 95% CIs. All analyses were performed using SPSS version 12 statistical software (SPSS Inc., Chicago, IL, USA). A two-tailed p value < 0.05 was considered significant for hypothesis testing.

Results

Baseline clinical, procedural and angiographic characteristics

Baseline characteristics are shown in Table 1 and 2. Baseline characteristics were comparable in the study population (n=100) and control group (n=193). The majority of patients were male, slightly overweight, with hypertension and/or hypercholesterolemia. Nearly half of the population had had a previous MI and were admitted to the hospital with the diagnosis of stable angina. Among DM patients, 56% had IDDM and mean EuroSCORE was 6.2±3.74.

Table 2. Angiographic and procedural characteristics, n(%).

	DM (n=100)	nonDM (n=193)	p value
Lesion location			
Ostium/shaft	21(21)	61(31.6)	0.56
Distal	79(79)	132(68.4)	0.07
DES			
Cypher	61(61)	95(49.2)	0.09
Taxus	39(39)	98(50.8)	0.09
Approach			
Single stent	56(56)	114(59.1)	0.61
Multiple stent	44(44)	79(40.9)	0.61
Stenting technique			
Provisional	56(56)	114(59.1)	0.61
V stenting	8(8)	15(7.8)	0.94
T stenting	5(5)	7(3.6)	0.57
Crushing	26(26)	49(25.4)	0.9
Culotte	5(5)	8(4.1)	0.73
Multivessel treatment	50(50)	94(48.7)	0.86
Stents per patient	1.51±0.61	1.45±0.57	0.43
Stent diameter (mm)	3.22±0.3	3.25±0.32	0.49
Stent length (mm)	18.4±7.1	17.3±7.3	0.2
Pre-dilation	68(68)	112(58)	0.19
Thrombectomy	2(2)	1(0.5)	0.59
Cutting	9(9)	18(9.3)	0.91
Rotablator	3(3)	4(2.1)	0.62
Atherectomy	1(1)	4(2.1)	0.5
Post-dilation	79(79)	144(74.6)	0.45
Maximal inflation pressure (atm)	16.7±3.1	16.9±2.6	0.68
Final kissing	44(44)	74(38.3)	0.68
Bigger balloon size (mm)	3.5±0.46	3.5±0.59	0.61
Post procedural RVD (mm)	3.78±0.54	3.69±0.56	0.48
Post procedural MLD (mm)	3.41±0.53	3.27±0.6	0.23
Angiographic FU	73(73)	131(67.9)	0.36

DM: diabetic patients; nonDM: non diabetic patients (control group); DES: drug-eluting stent; RVD: reference vessel diameter; MLD: minimum lumen diameter; FU: follow-up.

In both groups, approximately 75% of all lesions were distal and 40% of these were treated with a double stent approach. The favoured stenting technique was crush stenting. During the same period, a total of 680 patients with significant ULMCA disease underwent CABG in the seven participating centres.

Follow-up clinical outcomes

Short and long-term clinical outcomes are summarised in Table 3. All patients were followed for at least 36 months (range: from 36 to 57). No major differences in clinical outcome were found between the two groups at 30 days FU. Conversely, at 1-year, the incidence of CD, TLR, TVR and MACE was significantly higher in the DM group, compared to the controls. At 3-years FU, the incidence of overall death was 13% in the DM group and 7.2% in the non DM group (p=0.04). The incidence of TLR, TVR and MACE remained significantly higher in the study group but CD failed to reach statistical significance (p=0.058).

Adjusted curves derived from Cox survival analysis are displayed in Figure 1 (panels A-D). Freedom from MACE was 63.4% in the DM group and 77.6% in the controls (p<0.001) but freedom from CD&MI, TLR and TVR did not differ significantly between groups.

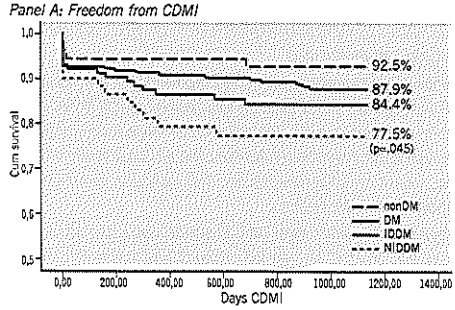
When divided into IDDM and NIDDM sub-groups, IDDM but not NIDDM patients had significantly lower freedom from CDMI, TLR, TVR and MACE compared to controls.

Table 3. Incidence of adverse events.

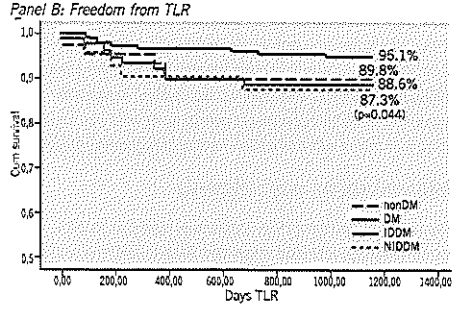
		DM (n=100)	nonDM (n=193)	p value
In-hospital	CD	1(1)	1(0.5)	0.45
	MI	3(3)	3(1.6)	0.22
	TLR	0(0)	0(0)	NA
	TVR	0(0)	1(0.5)	0.65
	MACE	3(3)	4(2.1)	0.26
30 days	CD	2(2)	2(1)	0.3
	MI	3(3)	3(1.6)	0.22
	TLR	1(1)	0(0)	0.34
	TVR	0(0)	1(0.5)	0.65
	MACE	5(5)	6(3.1)	0.17
6 months	CD	4(4)	3(1.6)	0.13
	MI	3(3)	3(1.6)	0.22
	TLR	4(4)	4(2.1)	0.18
	TVR	7(7)	5(2.6)	0.05
	MACE	15(15)	12(6.2)	0.009
1 year	CD	8(8)	5(2.6)	0.03
	MI	3(3)	4(2.1)	0.26
	TLR	7(7)	6(3.1)	0.07
	TVR	12(12)	10(5.2)	0.02
	MACE	24(24)	22(11.4)	0.003
3 years	CD	10(10)	10(5.2)	0.058
	MI	3(3)	7(3.6)	0.26
	TLR	10(10)	9(4.7)	0.04
	TVR	15(15)	17(8.8)	0.04
	MACE	31(31)	35(18.1)	0.005

DM: diabetic patients; nonDM: non diabetic patients (control group); CD: cardiac death; MI: myocardial infarction; TLR: target lesion revascularisation; TVR: target vessel revascularisation; MACE major adverse cardiac events (MACE are reported hierarchically).

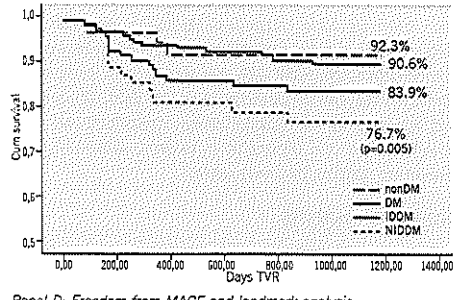
Panel A: Freedom from CDMI



Panel B: Freedom from TLR



Panel C: Freedom from TVR



Panel D: Freedom from MACE and landmark analysis

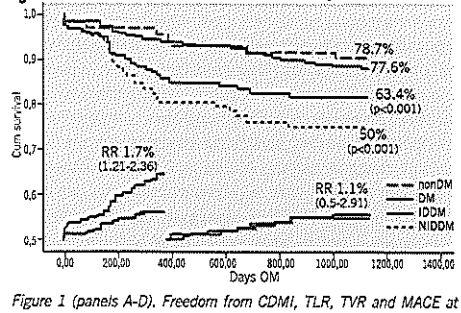


Figure 1 (panels A-D). Freedom from CDMI, TLR, TVR and MACE at means of covariates. The nonDM subgroup was taken as reference group. P values, derived from the comparison between each subgroup with nonDM, are shown only when statistical significance was reached.

Multiple variable analyses

Results of multiple variable analyses are presented in Table 4. Of note, IDDM was identified as an independent predictor for CD, TVR, TLR and MACE. EuroSCORE predicted CD and MACE, and hypercholesterolaemia, current smoking and stent diameter predicted MI, TVR and TLR, respectively.

Discussion

The main findings of the present study are the following: 1) long-term freedom from CD and MI of diabetic patients undergoing PCI for ULMCA disease are for the first time reported; 2) diabetic patients had a significantly higher incidence of MACE, compared to non-DM patients and this primarily reflects a higher TVR rate; 3) the majority of adverse events occurred within the first year and thereafter the event rate tended to stabilise over time; 4) IDDM patients had significantly worse clinical outcome compared to NIDDM and non-DM patients.

Diabetes mellitus plays a major role in the development and progression of coronary artery disease. Proposed mechanisms to explain the increased severity of CAD and poorer outcomes after PCIs in diabetic patients include a heightened inflammatory response, endothelial dysfunction, increased plaque burden and altered coagulation processes[11-14]. Introduction of DES has dramatically reduced the rate of stent restenosis and broadened the indications for PCI. This advance has shifted many subsets of patients with complex angiographic disease into the realm of percutaneous revascularisation and away from CABG. Previous large studies of diabetic patients have associated DES implantation with favourable mid-term clinical and angiographic results[2,15-17]. However, the impact of DES on very long-term clinical outcome is still largely unknown. Furthermore, the efficacy of these devices in diabetic patients undergoing PCI for significant ULMCA disease has not been established.

For the first time, the present results indicate that DES implantation in diabetic patients with ULMCA disease is feasible and effective over time. Notwithstanding the higher risk profile of our cohort (mean EuroSCORE 6.2±3.74), freedom from CD and MI was comparable with that of a previously reported study in diabetics with other subsets of lesions[18,19]. Consistent with these results, freedom from TLR in the DM patients was not significantly different from the control group, confirming the results of previous IVUS studies in which DES led to similar results both in DM and non-DM patients[20,21]. The presence of left main coronary artery disease, especially when it is not associated with other vessel disease, does not appear to increase the risk of adverse events. We speculate that large vessel size together with prolonged dual antiplatelet therapy that is usually prescribed to these patients may partially mitigate adverse responses previously determined in these patients after PCI.

Diabetic patients had significantly higher 1-year MACE rates compared with non diabetic patients. This was mostly driven by a higher rate of TVR. These results are in line with the ARTS II diabetic sub-study findings[22] and confirm the tendency in this subset of patients to develop new lesions and to have faster progression and more complex patterns of disease[23,24].

Previous studies have associated paclitaxel-eluting stents with a significant reduction in MACE in diabetic patients when compared to sirolimus. This advantage was hypothesised to be related to the different pathways targeted by the two compounds, which, in the case of paclitaxel was not affected by insulin-resistance[25]. Although in our study the sample size for this comparison is small, when tested in the multivariable model, SES and PES did not differ in efficacy. Although the "aggressiveness" of CAD in diabetic patients is indisputable, the relatively high incidence of MACE in this population could be also a matter of definitions. In fact, it is worth noting that in the context of LMCA disease, the TVR definition comprises the whole left coronary system and therefore the likelihood of a re-intervention due to a new lesion is much higher in this subset when compared to populations with multivessel disease. The survival curves showed that adverse events mainly occurred within the first 12 months, while thereafter the curves progressively flattened. This tendency was particularly evident in the DM group, in which 77.4% of all MACEs occurred within the first year of follow-up. Moreover, the landmark analysis showed a significantly increased risk ratio for incidence of MACE in the DM patients relative to the non-DM group at one year. Our results, though underpowered to

Table 4. Independent predictors of adverse events.

	CD	MI	TVR	TLR	MACE
IDDM	HR=4.597 (1.159-18.237) p=0.03		HR=3.678 (1.123-12.044) p=0.031	HR=11.454 (2.053-63.914) p=0.005	HR=2.590 (1.581-4.244) p<0.001
Current smoking			HR=2.873 (1.039-7.943) p=0.042		
Hypercholesterolaemia		HR=4.487 (1.365-14.749) p=0.013			
EuroSCORE	HR=1.336 (1.22-1.46) p<0.001				HR=1.063 (1.001-1.128) p=0.047
Stent diameter				HR=1.524 (1.326-2.687) p=0.002	

CD: cardiac death; MI: myocardial infarction; TLR: target lesion revascularisation; TVR: target vessel revascularisation; MACE major adverse cardiac events; IDDM: insulin-dependent diabetes mellitus

detect these differences, are consistent with findings in previous studies that identify diabetes as a strong independent predictor of progression of atheroma burden[23,24]. Based on our findings, diabetic patients with ULMCA disease undergoing PCI with DES implantation should be followed closely, and especially during the first year after the procedure.

In the present study, adverse outcome comprising CDMI, TLR, TVR as well as MACE was significantly increased in diabetics treated with insulin. In contrast, NIDDM patients had clinical outcomes that were not significantly different from the control group. This finding, which is consistent with prior reports[19,26-28], has several potential explanations. These include direct effects of exogenous insulin on neointimal proliferation and expression on IL-6 and TNF[29,30]. Furthermore, type II diabetic patients may have more severe cardiovascular disease at the time when insulin treatment is instituted[31,32].

At 3-year follow up, 50% of IDDM patients experienced an adverse event. In IDDM patients that underwent surgical revascularisation, the 5-year incidence of death was 12.2%[33] while the incidence of MACE was 25%[34]. Though limited, these results suggest that major improvements in DES technology and pharmacotherapy are still required to improve clinical outcome and that the decision to perform percutaneous revascularisation in this subset of patients should be decided cautiously and on a case by case basis.

Limitations

The present study was designed as a retrospective multicentre registry and therefore lacks randomisation and intention-to-treat data. Since no sample size calculations were performed, we acknowledge that our results may be affected by a type II error. Moreover, information on HbA1c is missing and its potential impact on clinical outcomes could not be evaluated.

References

1. Abizaid A, Costa MA, Blanchard D, Albertal M, Eltchaninoff H, Guagliumi G, Geert-Jan L, Abizaid AS, Sousa AG, Wuelfert E, Wietze L, Sousa JE, Serruys PW, Morice MC; Ravel Investigators. Sirolimus-eluting stents inhibit neointimal hyperplasia in diabetic patients. Insights from the RAVEL Trial. *Eur Heart J* 2004;25:107-112.

2. Moussa I, Leon MB, Baim DS, O'Neill WW, Popma JJ, Buchbinder M, Midwall J, Simonton CA, Kelm E, Wang P, Kuntz RE, Moses JW. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (SIRolImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. *Circulation* 2004;109:2273-2278.

3. Hermiller JB, Raizner A, Cannon L, Gurbel PA, Kutcher MA, Wong SC, Russell ME, Ellis SG, Mehran R, Stone GW. Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: the TAXUS-IV trial. *J Am Coll Cardiol* 2005;45:1172- 1179.

4. Lincoff AM. Important triad in cardiovascular medicine: diabetes, coronary intervention, and platelet glycoprotein IIb/IIIa receptor blockade. *Circulation* 2003;107:1556-1559.

5. Aronson D, Bloomgarden Z, Rayfield EJ. Potential mechanisms promoting restenosis in diabetic patients. *J Am Coll Cardiol* 1996;27:528-535.

6. Kurbaan AS, Bowker TJ, Ilsley CD, Sigwart U, Richards AF; on behalf of the CABRI Investigators (Coronary Angioplasty versus Bypass Revascularization Investigation). Difference in the mortality of the CABRI diabetic and non diabetic populations and its relation to coronary artery disease and the revascularization mode. *Am J Cardiol* 2001;87:947-50.

7. BARI Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. *N Engl J Med* 1996;335:217-25.

8. BARI Investigators. Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. *J Am Coll Cardiol* 2000;35: 1122-9.

9. Abizaid A, Costa MA, Centemero M, Abizaid AS, Legrand VM, Limet RV, Schuler G, Mohr FW, Lindeboom W, Sousa AG, Sousa JE, van Hout B, Hugenholtz PG, Unger F, Serruys PW; Arterial Revascularization Therapy Study Group. Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary artery disease: insights from the Arterial Revascularization Therapy Study (ARTS) trial. *Circulation* 2001;104:533- 8.

10. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007 May 1;115(17):2344-51.

11. Kastrati A, Schömig A, Elezi S, Schühlen H, Dirschinger J, Hadamitzky M, Wehinger A, Hausleiter J, Walter H, Neumann FJ. Predictive factors of restenosis after coronary stent placement. *J Am Coll Cardiol* 1997;30:1428-36

12. Smith SC Jr, Faxon D, Cascio W, Schaff H, Gardner T, Jacobs A, Nissen S, Stouffer R. Prevention conference VI: diabetes and cardiovascular disease: writing group VI: revascularization in diabetic patients. *Circulation* 2002;105:165-9.

13. Dibra A, Kastrati A, Mehilli J, Pache J, Schühlen H, von Beckerath N, Ulm K, Wessely R, Dirschinger J, Schömig A; ISAR-DIABETES Study Investigators. Paclitaxel-eluting or sirolimus eluting stents to prevent restenosis in diabetic patients. *N Engl J Med* 2005;353:663-70.

14. Elezi S, Kastrati A, Pache J, Wehinger A, Hadamitzky M, Dirschinger J, Neumann FJ, Schömig A.Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. *J Am Coll Cardiol* 1998;32:1866-73.

15. Iijima R, Ndrepepa G, Mehilli J, Markwardt C, Bruskina O, Pache J, Ibrahim M, Schömig A, Kastrati A. Impact of diabetes mellitus on long-term outcomes in the drug-eluting stent era. *Am Heart J.* 2007 Oct;154(4):688-93.

16. Hermiller JB, Raizner A, Cannon L, Gurbel PA, Kutcher MA, Wong SC, Russell ME, Ellis SG, Mehran R, Stone GW. Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: the TAXUS-IV trial. *J Am Coll Cardiol* 2005;45:1172-1179.

17. Valgimigli M, Chieffo A, Lefèvre T, Colombo A, Morice MC, Serruys PW. Revisiting the incidence and temporal distribution of cardiac and sudden death in patients undergoing elective intervention for unprotected left main coronary artery stenosis in the drug eluting stent era. A pooled analysis on 340 patients treated at three European referral centres. *EuroInterv.* 2007;2:435-443.

18. Briguori C, Condorelli G, Airoldi F, Focaccio A, D'Andrea D, Cannavale M, Abarghouei AA, Giordano S, De Vivo F, Ricciardelli B, Colombo A. Comparison of coronary drug-eluting stents versus coronary artery bypass grafting in patients with diabetes mellitus. *Am J Cardiol.* 2007 Mar 15;99(6):779-84.

19. Stankovic G, Cosgrave J, Chieffo A, Iakovou I, Sangiorgi G, Montorfano M, Airoldi F, Carlino M, Michev I, Finci L, Colombo A. Impact

of sirolimus-eluting and Paclitaxel-eluting stents on outcome in patients with diabetes mellitus and stenting in more than one coronary artery. *Am J Cardiol.* 2006 Aug 1;98(3):362-6. Epub 2006 Jun 12.

20. Sakurai R, Ako J, Morino Y, Sonoda S, Kaneda H, Terashima M, Hassan AH, Leon MB, Moses JW, Popma JJ, Bonneau HN, Yock PG, Fitzgerald PJ, Honda Y; SIRIUS Trial Investigators. Predictors of edge stenosis following sirolimus-eluting stent deployment (a quantitative intravascular ultrasound analysis from the SIRIUS trial). *Am J Cardiol.* 2005 Nov 1;96(9):1251-3.

21. Mintz GS. Features and parameters of drug-eluting stent deployment discoverable by intravascular ultrasound. *Am J Cardiol.* 2007 Oct 22;100(8B):26M-35M.

22. Macaya C, Garcia-Garcia HM, Colombo A, Morice MC, Legrand V, Kuck KH, Sheiban I, Suttorp MJ, Carrie D, Vrolix M, Wittebols K, Stoll HP, Donohoe D, Bressers M, Serruys PW. One-year results of coronary revascularization in diabetic patients with multivessel coronary artery disease. Sirolimus stent vs. coronary artery bypass surgery and bare metal stent: insights from ARTS I and ARTS I. *Eurointerv.* 2006;2:69-76.

23. Nicholls SJ, Tuzcu EM, Crowe T, Sipahi I, Schoenhagen P, Kapadia S, Hazen SL, Wun CC, Norton M, Ntanios F, Nissen SE. Relationship between cardiovascular risk factors and atherosclerotic disease burden measured by intravascular ultrasound. *J Am Coll Cardiol.* 2006;47(10):1967-75.

24. Nicholls SJ, Tuzcu EM, Sipahi I, Grasso AW, Schoenhagen P, Hu T, Wolski K, Crowe T, Desai MY, Hazen SL, Kapadia SR, Nissen SE. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA.* 2007 Feb 7;297(5):499-508.

25. Daemen J, Garcia-Garcia HM, Kukreja N, Imani F, de Jaegere PP, Sianos G, van Domburg RT, Serruys PW. The long-term value of sirolimus- and paclitaxel-eluting stents over bare metal stents in patients with diabetes mellitus. *Eur Heart J.* 2007 Jan;28(1):26-32.

26. Kumar R, Lee TT, Jeremias A, Rulsi CP, Sylvia B, Magallon J, Kirtane AJ, Bigelow B, Abrahamson M, Pinto DS, Ho KK, Cohen DJ, Carrozza JP Jr, Cutlip DE. Comparison of outcomes using sirolimus-eluting stenting in diabetic versus nondiabetic patients with comparison of insulin versus non-insulin therapy in the diabetic patients. *Am J Cardiol.* 2007 Oct 15;100(8):1187-91.

27. Orlic D, Bonizzoni E, Stankovic G, Airoldi F, Chieffo A, Corvaja N, Sanglorgi G, Ferraro M, Briguori C, Montorfano M, Carlino M, Colombo A. Treatment of multivessel coronary artery disease with sirolimus-eluting stent implantation: immediate and mid-term results. *J Am Coll Cardiol.* 2004 Apr 7;43(7):1154-60.

28. Ong AT, Aoki J, van Mieghem CA, Rodriguez Granillo GA, Valgimigli M, Tsuchida K, Sonnenschein K, Regar E, van der Giessen WJ, de Jaegere PP, Sianos G, McFadden EP, de Feyter PJ, van Domburg RT, Serruys PW. Comparison of short- (one month) and long- (twelve months) term outcomes of sirolimus- versus paclitaxel-eluting stents in 293 consecutive patients with diabetes mellitus (from the RESEARCH and T-SEARCH registries). *Am J Cardiol.* 2005 Aug 1;96(3):358-62.

29. Foster E, Zhang S, Kahn AM. Insulin stimulates arterial neointima formation in normal rats after balloon injury. *Diabetes Obes Metab* 2006;8:348 -351.

30. Krogh-Madsen R, Plomgaard P, Keller P, Keller C, Pedersen BK. Insulin stimulates interleukin-6 and tumor necrosis factor-alpha gene expression in human subcutaneous adipose tissue. *Am J Physiol Endocrinol Metab* 2004;286:E234 -E238.

31. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. *Diabetologia* 2003;46:3-19.

32. Scheen AJ, Legrand D. Platelet dysfunction associated with insulin therapy in patients with type 2 diabetes: please do not throw the baby out with the bathwater! *J Am Coll Cardiol* 2007;49:628-629.

33. Rodriguez AE, Baldi J, Fernandez Pereira C, Navia J, Rodriguez Alemparte M, Delacasa A, Vigo F, Vogel D, O'Neill W, Palacios IF. Five-year follow-up of the Argentine randomized trial of coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple vessel disease (ERACI II). *J Am Coll Cardiol.* 2005;46(4):582-588.

34. Serruys PW, Ong AT, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJ, Schonberger JP, Buller N, Bonser R, Disco C, Backx B, Hugenholtz PG, Firth BG, Unger F. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol.* 2005;46(4):575-581.

CHAPTER 5

PERCUTANEOUS CORONARY INTERVENTION OR CORONARY ARTERY BYPASS GRAFT FOR UNPROTECTED LEFT MAIN CORONARY ARTERY DISEASE: THE ENDLESS DEBATE

with revascularization up to 24 months, and in the TOSCA-2 (Total Occlusion Study of Canada) trial (24), a substudy of the OAT study, there was a trend toward more favorable remodeling.

The results of the OAT study do not prove or disprove the benefits of late revascularization in patients similar to the patients in the OAT study and certainly do not apply to the entirety of post-AMI patients. Unfortunately, despite the efforts of investigators like the OAT Investigators, only 3,560 patients have been randomized to date, and they may not be enough to draw meaningful conclusions and/or identify subgroups of patients with greatest benefit or risk from late revascularization.

We thank Dr. Džavík and colleagues for this opportunity to clarify that our analysis was not designed to prove or disprove the findings of the OAT study, which likely applies to a minority of patients after AMI. Instead, we set out to analyze all available evidence and demonstrated the benefit of late revascularization of the IRA late after AMI.

***Antonio Abbate, MD**
Giuseppe G. L. Biondi-Zoccai, MD
Darryn L. Appleton, MBChB
Paul Erne, MD
Andreas W. Schoenenberger, MD
Michael J. Lipinski, MD
Piefrancesco Agostoni, MD
Imad Sheiban, MD
George W. Vetrovec, MD

*Virginia Commonwealth University
Department of Medicine
10025 Bellona Court
Richmond, Virginia 23233
E-mail: abbatea@yahoo.com

doi:10.1016/j.jacc.2008.05.015

REFERENCES

1. Abbate A, Biondi-Zoccai GGL, Appleton DL, et al. Survival and cardiac remodeling benefits in patients undergoing percutaneous coronary intervention of the infarct-related artery: evidence from a meta-analysis of randomized controlled trials. J Am Coll Cardiol 2008;51:956–64.
2. Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival. Should the paradigm be expanded? Circulation 1989;79:441–4.
3. Hochman JS, Lamas GA, Buller CE, et al. Coronary intervention for persistent occlusion after myocardial infarction. N Engl J Med 2006; 355:2395–407.
4. Erne P, Schoenenberger AW, Burckhardt D, et al. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction. The SWISSI II randomized controlled trial. JAMA 2007; 297:1985–91.
5. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324: 71–86.
6. Eysenck HJ. An exercise in mega-silliness. Am Psychol 1978;33:517.
7. Hunt MM. How science takes stock: the story of meta-analysis. New York, NY: Russell Sage Foundation, 1999.
8. Eysenck HJ. Meta-analysis: sense or non-sense? Pharmaceutical Medicine 1992;6:113–9.
9. Eysenck HJ. Meta-analysis: an abuse of research integration. J Spec Educ 1984;18:41–59.
10. Glass GV. Primary, secondary, and meta-analysis of research. Educ Res 1976;5:3–8.
11. Zeymer U, Uebis R, Vogt A, et al. Randomized comparison of percutaneous transluminal coronary angioplasty and medical therapy in stable survivors of acute myocardial infarction with single vessel disease: a study of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausaerzte. Circulation 2003;108:1324–8.
12. Biondi-Zoccai GGL, Abbate A, Agostoni P, et al. Long-term benefits of an early invasive management in acute coronary syndromes depend on intracoronary stenting and aggressive antiplatelet treatment: a metaregression. Am Heart J 2005;149:504–11.
13. Ioannidis JP, Katritsis DG. Percutaneous coronary intervention for late reperfusion after myocardial infarction in stable patients. Am Heart J 2007;154:1065–71.
14. Appleton D, Abbate A, Biondi-Zoccai GG, et al. Revisiting the role of percutaneous revascularization versus medical therapy for later infarct-related artery occlusion. Am Heart J 2008;155:e41.
15. Yousef ZR, Redwood SR, Bucknall CA, Sulke AN, Marber MS. Late intervention after anterior myocardial infarction. Effects on left ventricular size, function, quality of life, and exercise tolerance: Results of The Open Artery Trial (TOAT study). J Am Coll Cardiol 2002;40: 869–76.
16. Appleton DL, Abbate A, Biondi-Zoccai GGL. Late percutaneous coronary intervention for the totally occluded infarct-related artery — a meta-analysis of the effects on cardiac function and remodeling. Cathet Cardiovasc Interv 2008;71:772–81.
17. Bellenger NG, Yousef Z, Rajappan K, Marber MS, Pennell DJ. Infarct zone viability influences ventricular remodeling after late recanalisation of an occluded infarct related artery. Heart 2005;91:478–83.
18. Topol EJ, Califf RM, Vandormael M, et al. A randomized trial of late reperfusion therapy for acute myocardial infarction. Thrombolysis and Angioplasty in Myocardial Infarction-6 Study Group. Circulation 1992;85:2090–9.
19. Schoemig A, Mehilli J, Antoniucci D, et al. Mechanical reperfusion in patients with acute myocardial infarction presenting more than twelve hours from symptom onset. JAMA 2005;293:2865–72.
20. Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin Epidemiol 2006;59:7–10.
21. Thiessen Philbrook H, Barrowman N, Garg AX. Imputing variance estimates do not alter the conclusions of a meta-analysis with continuous outcomes: a case study of changes in renal function after living kidney donation. J Clin Epidemiol 2007;60:228–40.
22. J Wittes. Times to event: why are they hard to visualize? J Natl Cancer Inst 2008;100:80–2.
23. Bollschweiller E. Benefits and limitations of Kaplan-Meier calculations of survival chance in cancer surgery. Langenbecks Arch Surg 2003;388:239–44.
24. Džavík V, Buller CE, Lamas GA, et al., TOSCA-2 Investigators. Randomized trial of percutaneous coronary intervention for subacute infarct-related coronary artery occlusion to achieve long-term patency and improve ventricular function. The Total Occlusion Study of Canada (TOSCA)-2 trial. Circulation 2006;114:2449–57.

Percutaneous Coronary Intervention or Coronary Artery Bypass Graft for Unprotected Left Main Coronary Artery Disease: The Endless Debate

The "state-of-the art" paper written by Taggart et al. (1) calls into question the current evidence in support of percutaneous coronary intervention (PCI) for the treatment of unprotected left main stem disease. In view of the fact that current guidelines still indicate coronary artery bypass grafting (CABG) as the "standard of care," the authors conclude that the use of drug-eluting stents (DES) in "off-label" cases should be discouraged and that good surgical

candidates with unprotected left main coronary artery (ULMCA) disease should undergo surgical revascularization. These conclusions, although absolutely reasonable, raise 2 questions: 1) Is CABG really proven to perform better than PCI in this subset of patients? 2) Is CABG to be recommended in all good surgical candidates?

In an attempt to justify their conclusion, the authors presented 6 studies conducted in patients with ULMCA disease who had undergone CABG. Of note, none of these studies had clinical follow-up periods of longer than 2 years, and only 2 out of 6 had a clinical follow-up longer than 1 year (Lu et al. [2] and Yeatman et al. [3]). The mortality rate of 5% to 6% reported by these studies is truly encouraging. However, the authors did not mention the impressive occurrence of post-procedural morbidity in these patients. In the study conducted by Lu et al. (2) on 1,197 patients who underwent CABG for ULMCA, the rates of in-hospital adverse events were the following: mortality 2.8%, renal failure 3.9%, gastrointestinal complications 3.6%, stroke 2.2%, post-procedural myocardial infarction 7.1%, reoperation for bleeding 2.8%, sternal wound infection 4.2%, chest infection 5.3%, ventilation >48 h 6%, stay after operation >14 days 9.3%. The incidence of death in patients undergoing CABG for ULMCA disease was reported to be 11.3% at 1 year in the Cleveland Clinic Foundation Data (4), 12.8% at 3 yeas in the New York Bypass Surgery Registry (5), 13.2% at 5 years in the study conducted by d'Allonnes et al. (6), and 22.6% at 5 years in the Duke Cardiology Database (7). These results are far worse than those reported by the authors and do not appear to be superior to those reported in several PCI studies.

In discussing the experience with bare-metal stents (BMS), the authors presented the results from earlier PCI studies that enrolled almost exclusively high-risk patients. The "poor" late outcomes after ULMCA stenting with BMS are compared with the excellent results obtained in the SoS (Stent or Surgery) trial. This comparison of "apples versus pears," i.e., left main disease in high-risk patients versus 2- to 3-vessel disease in stable patients, is not a proper scientific argument. In that specific study, the comparison between CABG and PCI resulted in no statistically significant differences in terms of death, myocardial infarction, or stroke at 1-year follow-up (8). With regard to DES implantation, the authors describe a selection of studies that presents an important nonhomogeneity in terms of trial design: consecutive (e.g., Valgimigli et al. [9], Lee et al. [10]) vs. selective (de Lezo et al. [11]) patient enrollment and, in some studies, the use of DES was not exclusive (e.g., approximately 40% of patients from the Bologna Registry received BMS). Moreover, the authors did not take into account the importance and influential outcomes of the various stenting techniques used for distal left main disease.

It therefore seems difficult to draw any conclusions from the pooling of these results and, furthermore, compare them with the outcomes obtained in the surgical literature. In the DELFT (Drug Eluting stent for LeFT main) registry (12), the 3-year incidence of cardiac death, target vessel revascularization, and major adverse cardiovascular events (MACE) in the elective subgroup was 6.2%, 16%, and 30.5%, respectively. Recent studies conducted on patients with ULMCA who underwent surgical revascularization reported a similar incidence of death, a lower incidence of TVR, but an apparently greater incidence of MACE (9,13).

Additionally, it was noted by the authors that distal left main disease is a major and independent predictor of MACE at mid-term follow-up (9) and argued that: "the precise anatomical location and complexity of left main stenosis . . . have negligible influence on the success of CABG." Two issues deserve further clarification with respect to this statement: 1) In patients undergoing PCI, distal left main disease is associated with a higher risk for reintervention but not necessarily death or myocardial infarction, which are predominantly affected by surgical risk status. 2) To the best of our knowledge, there are no data supporting the notion that outcomes after surgery are not affected by the location of the lesion within the left main stem. Distal left main disease may simply be a marker of severe, diffuse coronary disease and, as such, carry with it a worse prognosis irrespective of the final revascularization strategy.

In all major institutions, current standard approach to patients presenting with significant ULMCA disease is to have them evaluated by both interventional cardiologists and cardiac surgeons and to reach the decision to opt for PCI or surgery by consensus, on the basis of: 1) hemodynamic conditions; 2) lesion characteristics; 3) vessel size; 4) the presence of comorbidities; 5) quality of arterial and/or venous conduits for grafting; and 6) patient and/or referring physician preferences. Patients are always fully informed about the potential risks and outcomes of both the surgical and the percutaneous approaches. Stating that "patients are influenced into making a pre-ordained choice" and that cardiologists "instigate" patients in making these choices is speculative.

Should all good candidates for surgery go to surgery and poor candidates to PCI? So far, there is no strong evidence that one approach is better than the other in terms both of clinical outcomes and quality of life (QoL). A recent meta-analysis by Bravata et al. (14) of 23 randomized controlled trials showed no difference between PCI and CABG in terms of mortality at 10 years' follow-up. Health-related QoL is of particular value in coronary artery disease, because the objective of intervention is not only to avoid clinical adverse outcomes but also to relieve symptoms and improve function and ability to participate in daily activities. Long-term studies comparing QoL related to these 2 therapeutic strategies are not available but the results coming from the available literature reported so far no major differences (15–18).

Current guidelines still recommend surgical revascularization as the primary procedure in ULMCA patients, but considering them as "the body of criminal law" is not always appropriate. Guidelines are dynamic and in constant flux and have to be updated according to new evidences coming from clinical experience, and not vice-versa. It is important to realize that new-generation DES approved for clinical use, new technical strategies, and prolonged dual-antiplatelet treatment have significantly decreased the risk of adverse events (including late in-stent thrombosis) after PCI.

Randomized clinical trials are necessary to shine a light on this endless debate. The LEMANS trial (19) is the only reported randomized trial comparing PCI versus CABG for ULMCA disease. The increased short-term complication rate in the CABG group appeared to be minimized by stressing similar 1-year MACE results in the 2 groups. Moreover, no late in-stent thrombosis occurred both in the BMS and in the DES groups, demonstrating that percutaneous treatment of ULMCA is safe. Results of the complete SYNTAX (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries) study, which enrolled 700 randomized patients with ULMCA disease, will be presented at the 2008 European Society of Cardiology congress. Until then, judicious individual assessment of each patient should prevail, that is to say, we should keep trying to

treat patients—that do not fit in the current recommendations—according our current clinical experience and judgment.

"On the mountains of truth you can never climb in vain: either you will reach a point higher up today, or you will be training your powers so that you will be able to climb higher tomorrow."
Friedrich Nietzsche (20)

Emanuele Meliga, MD
Marco Valgimigli, MD, PhD
Pawel Buszman, MD, FACC, FESC
***Patrick W. Serruys, MD, PhD, FACC, FESC**

*Director of the Interventional Cardiology Department
Thoraxcenter
Erasmus Medical Center
Erasmus University
Dr Molewaterplein 40, 3015 GD
Rotterdam, the Netherlands
E-mail: p.w.j.c.serruys@erasmusmc.nl

doi:10.1016/j.jacc.2008.04.048

REFERENCES

1. Taggart DP, Kaul S, Boden WE, et al. Revascularization for unprotected left main stem coronary artery stenosis: stenting or surgery. J Am Coll Cardiol 2008;51:885–92.
2. Lu JC, Grayson AD, Pullan DM. On-pump versus off-pump surgical revascularization for left main stem stenosis: risk adjusted outcomes. Ann Thorac Surg 2005;80:136–42.
3. Yeatman M, Caputo M, Ascione R, Ciulli F, Angelini GD. Off-pump coronary artery bypass surgery for critical left main stem disease: safety, efficacy and outcome. Eur J Cardiothorac Surg 2001;19:239–44.
4. Ellis SG, Hill CM, Lytle BW. Spectrum of surgical risk for left main coronary stenoses: benchmark for potentially competing percutaneous therapies. Am Heart J 1998;135:335–8.
5. Mehran T. DES for the Treatment of Left Main Disease. Paper presented at: TCT 2006; July 21, 2006; Washington, DC.
6. d'Allonnes FR, Corbineau H, Le Breton H, Leclercq C, Leguerrier A, Daubert C. Isolated left main coronary artery stenosis: long term follow up in 106 patients after surgery. Heart 2002;87:544–8.
7. Garcia E. Left Main. Paper presented at: EuroPCR; May 22, 2007; Barcelona, Spain.
8. Zhang Z, Mahoney EM, Spertus JA, et al. The impact of age on outcomes after coronary artery bypass surgery versus stent-assisted percutaneous coronary intervention: one-year results from the Stent or Surgery (SoS) trial. Am Heart J 2006;152:1153–60.
9. Valgimigli M, van Mieghem CA, Ong AT, et al. Short- and long-term clinical outcome after drug-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: (RESEARCH and T-SEARCH). Circulation 2005;111:1383–9.
10. Lee MS, Kapoor N, Jamal F, et al. Comparison of coronary artery bypass surgery with percutaneous coronary intervention with drug-eluting stents for unprotected left main coronary artery disease. J Am Coll Cardiol 2006;47:864–70.
11. de Lezo JS, Medina A, Pan M, et al. Rapamycin-eluting stents for the treatment of unprotected left main coronary disease. Am Heart J 2004;148:481–5.
12. Meliga E, Garcia-Garcia HM, Valgimigli M, et al. DELFT Registry. Longest available clinical outcomes after drug-eluting stent implantation for unprotected left main coronary artery disease: the DELFT (Drug Eluting stent for LeFT main) Registry. J Am Coll Cardiol 2008;51:2212–9.
13. Chieffo A, Morici N, Maisano F, et al. Percutaneous treatment with drug-eluting stent implantation versus bypass surgery for unprotected left main stenosis: a single-center experience. Circulation 2006;113:2542–7.
14. Bravata DM, Gienger AL, McDonald KM, et al. Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. Ann Intern Med 2007;147:703–16.
15. Wilhrborg P. Quality of life after coronary angioplasty or bypass surgery. 1-year follow-up in the Coronary Angioplasty versus Bypass Revascularization investigation (CABRI) trial. Eur Heart J 1999;20:635–6.
16. Kaul P, Armstrong PW, Fu Y, et al., GUSTO-IIb Investigators. Impact of different patterns of invasive care on quality of life outcomes in patients with non-ST elevation acute coronary syndrome: results from the GUSTO-IIb Canada-United States substudy. Can J Cardiol 2004;20:760–6.
17. Kamiya M, Takayama M, Takano H, et al. Clinical outcome and quality of life of octogenarian patients following percutaneous coronary intervention or surgical coronary revascularization. Circ J 2007;71:847–54.
18. Favarato ME, Hueb W, Boden WE, et al. Quality of life in patients with symptomatic multivessel coronary artery disease: a comparative post hoc analyses of medical, angioplasty or surgical strategies-MASS II trial. Int J Cardiol 2007;116:364–70.
19. Buszman PE, Kiesz SR, Bochenek A, et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. J Am Coll Cardiol 2008;51:538–45.
20. Human, All Too Human. 1878.

Reply

We are grateful to Dr. Meliga and colleagues for their interest in our article (1). They raise several important issues that we will address in a similar order.

The first issue deals with mortality and morbidity after coronary artery bypass grafting (CABG). As referenced in our article (1), the mortality for all 5,003 patients with left main stem stenosis undergoing CABG in the United Kingdom in 2003 was 3% (and <2% in 17,000 without left main stem [LMS] stenosis and 1% in 3,102 patients in the ART [Arterial Revascularisation] trial). Because enough is known about post-CABG complications, risk models have been developed to reliably predict their occurrence, whereas similar data are quite lacking in the percutaneous coronary intervention (PCI) domain.

In addition, although all postoperative morbidity is unsatisfactory, the reality is that, with the exception of stroke (1% to 2%), most of it is self-limiting and of little consequence to the patient over the long term. To equate early postoperative morbidity to the reduced survival and marked increase in the need for reintervention with PCI over the long term is arguably a false economy. Furthermore, long-term mortality from CABG (as well as PCI) may also reflect other co-existing morbidities, rather than being attributable to ischemic heart disease.

With regard to bare-metal stents, we stated explicitly that superior results were obtained in lower-risk patients and that, as for CABG, the results of PCI would also be disadvantaged by greater-risk patients. Although Dr. Meliga and colleagues state that there was no significant difference in mortality between CABG and PCI in the SoS (Stent or Surgery) trial at 1 year, it should be noted that, at 5-year follow-up in this study (2), there was a significant reduction in the risk of mortality with CABG (6.6%) versus PCI (10.9%), reinforcing the well-known observation that the benefit of CABG often accrues with time. We agree with Dr. Meliga and colleagues that substantial heterogeneity among drug-eluting stent trials precludes pooling them together. Accordingly, we did not perform a meta-analysis. Our aim was simply to present all the published studies in the literature.

The complexity and precise anatomical location of distal left main stem disease, along with its frequently associated multivessel coronary disease, is not relevant during CABG because bypass

CHAPTER 6

LONG-TERM CLINICAL AND ANGIOGRAPHIC OUTCOMES OF TREATMENT OF UNPROTECTED LEFT MAIN CORONARY ARTERY STENOSIS WITH SIROLIMUS-ELUTING STENTS

Long-Term Clinical and Angiographic Outcomes of Treatment of Unprotected Left Main Coronary Artery Stenosis With *Sirolimus*-Eluting Stents

Imad Sheiban, MD[a,*], Emanuele Meliga, MD[a], Claudio Moretti, MD[a], Giuseppe G.L. Biondi-Zoccai, MD[a], Giuseppe Rosano, MD, PhD[b], Filippo Sciuto, MD[a], Walter Grosso Marra, MD[a], Pierluigi Omedè, MD[a], Argyrios Gerasimou, MD[a], and Gian Paolo Trevi, MD[a]

Favorable early results of percutaneous drug-eluting stents in unprotected left main (LM) disease are available, but outcome data beyond 6 to 10 months are lacking. We evaluated the long-term results of sirolimus-eluting stents (SESs) in patients with LM disease. From November 2002 to December 2004, consecutive patients with LM disease, without contraindications to double antiplatelet therapy and undergoing SES implantation, were enrolled prospectively. The primary end point of the study was occurrence of major adverse cardiovascular events. In total 85 patients were treated with 118 SES and followed for 595 ± 230 days. Event-free survival rates at 1 year and 2 years were 85.5% and 78.6%, respectively. Only 2 deaths occurred overall (2.4%), the first in-hospital in a very high-risk patient according to the European System for Cardiac Operative Risk Evaluation and the second in a patient with severe systolic dysfunction already at the index procedure). Myocardial infarction was adjudicated in 3 patients (3.6%), 2 occurring periprocedurally and 1 during follow-up for a de novo nontarget lesion. There were 7 (10.8%) target lesion revascularizations at 24 months, with all but 1 percutaneous and in a subject with bifurcation LM disease at baseline. At 9-month angiography, late loss was 0.15 ± 0.81 mm and restenosis rate was 8.2%. An increased incidence of adverse events was noted in patients undergoing SES after dilation with extremely oversized balloons. No case of stent thrombosis was reported. In conclusion, this single-center experience suggests that percutaneous use of SESs to treat LM disease in unselected high-risk patients is safe and effective even 1 year after implantation. (Am J Cardiol 2007; 100:431–435)

Use of drug-eluting stents in real-life patients with unprotected left main (LM) disease is becoming more common, at least in selected centers,[1,2] despite the uncertainty on their long-term outlook.[3] It is thus pivotal to accurately appraise the outcome of sirolimus-eluting stent (SES) implantation after the conventional threshold for midterm follow-up (i.e., 6 to 12 months). Toward this aim, we conducted a prospective single-center observational study to assess the long-term safety and efficacy of SES implantation in patients with LM disease.

Methods

From a total population of 2,126 consecutive patients referred for coronary angiography to our institution (a tertiary academic care center with an annual caseload of >1,000 percutaneous coronary interventions) between November 2002 and December 2004 because of established or suspected coronary artery disease, we prospectively enrolled 85 consecutive patients (4.0%) with significant LM stenosis (≥50% diameter stenosis by visual estimate), coronary anatomy suitable for percutaneous revascularization, and undergoing SES implantation. SESs (the default drug-eluting stent in our center) were used without restrictions, i.e., in patients with chronic stable angina pectoris with documented myocardial ischemia and those with acute coronary syndromes (unstable angina pectoris, ST-elevation myocardial infarction, non–ST-elevation myocardial infarction). Only patients with contraindications for antiplatelet or anticoagulation therapy or allergy to sirolimus were excluded.

Patients were stratified into risk classes using the Parsonnet[4] and European System for Cardiac Operative Risk Evaluation (EuroSCORE)[5] systems. High-risk subjects were defined as those with a Parsonnet score ≥15 or EuroSCORE ≥6, and very high-risk patients as those with a Parsonnet score ≥20 or EuroSCORE ≥13. Notably, none of the included patients had absolute contraindications to bypass surgery. All patients were fully informed about the possible early and late risks of the procedure and of alternative management strategies, and written informed consent was obtained from all patients. All patients received pretreatment with low-molecular-weight heparin or unfractionated heparin, aspirin, and clopidogrel (75 mg/

[a]Interventional Cardiology, Division of Cardiology, University of Turin, Turin; and [b]Center for Clinical and Basic Research, IRCCS San Raffaele, Rome, Italy. Manuscript received February 1, 2007; revised manuscript received and accepted March 5, 2007.

*Corresponding author: Tel: 39-0116-336-026; fax: 39-0116-967-053.
E-mail address: isheiban@yahoo.com (I. Sheiban).

0002-9149/07/$ – see front matter
doi:10.1016/j.amjcard.2007.03.041

day begun ≥3 days before the procedure or 300-mg loading dose). Periprocedural use of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. After the procedure, patients received clopidogrel 75 mg/day for 6 months for patients with stable coronary disease at admission and 12 months for those with unstable coronary disease, and aspirin ≥75 mg indefinitely for all. The study complied with the Declaration of Helsinki, and formal ethics committee approval was waived because of the observational design.

Intravascular ultrasound was performed for lesions with inadequate visualization by angiography only (e.g., preprocedurally for highly eccentric but noncritical stenoses and periprocedurally to clarify the nature of luminal haziness). Predilation of the LM coronary artery was performed only in case of very tight or calcified lesions by using undersized conventional balloons. Stent deployment was achieved by inflating the delivery balloon at nominal pressure. Additional debulking devices (rotablator or cutting balloon) were used only in patients with fibrous/calcified lesions in which predilation with standard balloons failed. Stent overexpansion with high-pressure inflations with short noncompliant balloons was performed in those selected cases with suboptimal stent expansion by visual assessment, taking care not to determine geographic miss or edge dissection.[6] Regardless of lesion location, the LM artery was fully stented in all patients. Lesions involving the ostium or shaft without involvement of bifurcation (n = 33) were treated with a single stent, whereas lesions involving bifurcation (n = 52) were treated with 1 of the following procedures according to operator choice: stenting across the left circumflex coronary artery (n = 6), stenting across the left anterior descending ostium (n = 7), kissing stenting (i.e., V stenting; n = 8), or provisional T stenting (n = 31). In no cases were "crushing" and "culottes" techniques performed.[7,8] Final kissing balloon dilation was performed in all 52 patients with distal LM bifurcation lesion. Procedural success was defined as LM revascularization with a residual stenosis <30% at online quantitative coronary angiogram, without major procedural or postprocedural adverse events (death, myocardial infarction, or emergency target vessel revascularization). To ensure the safety and efficacy of revascularization procedures, all were performed by 2 experienced interventionists (IS and CM) with a personal caseload of >1,000 percutaneous coronary interventions and extensive experience in ancillary techniques (e.g., intravascular ultrasound and use of the Rotablator).

Quantitative coronary angiography was performed using dedicated software with an automated edge-detection system (Inturis Viewer 1.2, Philips Medical Image Packing System, Eindhoven, The Netherlands). For the purpose of this study, baseline, postprocedural, and follow-up quantitative coronary angiographies were performed offline. Minimal lumen diameter, percent diameter stenosis, reference vessel diameter, lesion length, acute gain, and late loss were evaluated.[9] Binary restenosis was defined as lumen decrease >50% at the segment site on quantitative angiogram, and the specific pattern of restenosis was adjudicated.[10] After discharge, patients were evaluated in the outpatient clinic from 30 to 40 days. Angiographic follow-up was scheduled after 6 to 9 months or sooner if driven by clinical symptoms or documented myocardial ischemia. Patients were then followed by outpatient visits or monthly telephone interviews. A final telephone interview or office visit was performed at the end of the follow-up period in every patient. Occurrence of adverse events was documented by hospital records or coroner report, with deaths categorized as due to cardiac and noncardiac causes. In particular, those deaths that were not classifiable but had no other underlying possible cause were considered cardiac.

The primary end point of the study was occurrence of major adverse cardiovascular events (MACE) at follow-up, defined as occurrence of death, nonfatal myocardial infarction, or target vessel revascularization (including target and nontarget lesion revascularizations). Myocardial infarction was defined as a creatine kinase-MB mass increase >3 times the upper limit of normal. Acute or subacute stent thrombosis was de-

Table 1
Baseline clinical characteristics (n = 85)

Age (yrs)	68 ± 10
Men	70 (82%)
Arterial hypertension	72 (85%)
Blood hypercholesterolemia	49 (58%)
Current smoking	20 (24%)
Noninsulin-dependent diabetes mellitus	9 (11%)
Insulin-dependent diabetes mellitus	9 (11%)
Chronic renal failure	3 (4%)
Peripheral artery disease	20 (24%)
Previous myocardial infarction	25 (29%)
Previous percutaneous coronary intervention	24 (28%)
Previous coronary artery bypass grafting	16 (19%)
Diagnosis at admission	
Stable angina pectoris	11 (13%)
Silent myocardial ischemia	11 (13%)
Acute pulmonary edema	1 (1%)
Unstable angina pectoris	40 (47%)
Non–ST-elevation myocardial infarction	6 (7%)
ST-elevation myocardial infarction	11 (13%)
Left ventricular ejection fraction (%)	55 ± 10
EuroSCORE	13 ± 5
Parsonnet score	12 ± 7

Table 2
Angiographic and procedural characteristics (n = 85)

Lesion location	
Ostium	14 (17%)
Shaft	20 (24%)
Bifurcation	52 (61%)
Multivessel coronary disease	75 (88%)
Multivessel coronary stenting	69 (81%)
Glycoprotein IIb/IIIa inhibitor use	30 (35%)
Intravascular ultrasound	9 (11%)
Intra-aortic balloon pump	7 (8%)
Rotational atherectomy	1 (1%)
Stents per patient	1.38 (118/85)
Stent diameter (mm)	3.21 ± 0.29
Stent length (mm)	14.1 ± 5.4
After dilatation (%)	55 (65)
Maximal inflation pressure (atm)	18.8 ± 2.8
Treatment for bifurcational lesions	
1 stent	24 (46%)
2 stents	28 (54%)
Final kissing balloon	52 (100%)

Table 3
Major adverse cardiovascular events during follow-up

Cumulative Rate of Adverse Events	In Hospital (n = 85)	3-mo Follow-up (n = 85)	6-mo Follow-up (n = 85)	12-mo Follow-up (n = 85)	24-mo Follow-up (n = 65)
Death	1 (1.2%)	1 (1.2%)	1 (1.2%)	2 (2.4%)	2 (3.1%)
Myocardial infarction	2 (2.4%)	2 (2.4%)	3 (3.6%)	3 (3.6%)	3 (4.6%)
Target lesion revascularization	0	0	2 (2.4%)	5 (6.0%)	7 (11%)
Target vessel revascularization	0	0	2 (2.4%)	5 (6.0%)	7 (11%)
Stent thrombosis	0	0	0	0	0
Stroke	0	0	0	0	0
Total MACES*	3 (3.5%)	3 (3.5%)	6 (7.1%)	10 (12%)	12 (19%)

* Defined as death, myocardial infarction, or target vessel revascularization.

fined as angiographic evidence of stent occlusion or cardiac death or myocardial infarction within 24 hours or 30 days, respectively, after the procedure.[11] Late stent thrombosis was defined as angiographic evidence of stent thrombosis, cardiac death, or myocardial infarction in the target territory (i.e., left anterior descending or left circumflex coronary artery) occurring 30 days to 6 months after the procedure. Very late stent thrombosis was defined as angiographic evidence of stent thrombosis or cardiac death or myocardial infarction in the target territory or myocardial infarction in the target territory occurring >6 months after the procedure.

Data are expressed as mean ± SD for continuous variables and as frequencies for categorical variables. Differences between groups were assessed using chi-square and Student's *t* tests. A 2-tailed p value <0.05 was considered statistically significant. Overall survival and survival free from MACEs were assessed according to the Kaplan-Meier method. Multivariable analysis was performed to detect clinical and angiographic variables related to acute and long-term events.

Table 4
Quantitative coronary angiography

Baseline angiography (n = 85)	
Reference vessel diameter (mm)	3.84 ± 0.46
Minimum lumen diameter (mm)	1.41 ± 0.46
Diameter stenosis (%)	62.1 ± 12.3
Postprocedural angiography (n = 85)	
Minimum lumen diameter (mm)	3.53 ± 0.35
Diameter stenosis (%)	9.4 ± 4.2
Acute gain (mm)	2.12 ± 0.49
Follow-up angiography (n = 71)	
Minimum lumen diameter (mm)	3.03 ± 0.83
Diameter stenosis (%)	18.9 ± 7.2
Late lumen loss (mm)	0.15 ± 0.81
Binary angiographic restenosis	
Overall	7 (10%)
Focal	6 (86%)
Diffuse	1 (14%)
Ostium or shaft lesions	1 (14%)
Bifurcation lesions	6 (86%)

Results

Baseline clinical and angiographic characteristics are listed in Tables 1 and 2. Patients' mean age was 68 ± 10 years; 24 patients (28%) patients had previous percutaneous coronary intervention on other coronary vessels, 20 (24%) had peripheral artery disease, and 4 (5%) chronic renal failure; and ejection fraction was 52 ± 10%. The principal clinical indication for referral was unstable angina in 40 (47%) followed by acute myocardial infarction in 17 (20%), with ST-elevation myocardial infarction in 11 (13%) and non–ST-elevation myocardial infarction in 6 (7%).

On baseline angiogram multivessel coronary artery disease was found in 75 patients (88%) and multivessel treatment was performed in 69 (92%). LM coronary lesions were located mainly at the bifurcation in 52 (61%), and a minority involved only the ostium (14, 16%) or the shaft (20, 23%). According to the EuroSCORE and Parsonnet scoring systems 29 patients (34%) were considered at high risk and 15 (17%) at very high risk. Lesions not involving bifurcation were treated with a single stent; distal lesions were treated with a single stent in 24 patients (43%) by a provisional T-stenting technique and with 2 stents in 28 patients (57%) using a modified T-stenting technique or V stenting. Baseline reference vessel diameter was 3.84 ± 0.46 mm, minimum lumen diameter was 1.41 ± 0.46 mm, and mean percent stenosis was 62.1 ± 12.3%. In total 118 SESs were implanted, with a stent diameter of 3.21 ± 0.29 mm and a stent length of 14.1 ± 5.4 mm.

Procedural details are listed in Table 2, and in-hospital events are presented in Table 3. Procedural success was obtained in 82 patients (97%), with intraprocedural death occurring in 1 patient (1%) and postprocedural non–Q-wave myocardial infarction in 2 patients (2%). No patient had acute in-stent thrombosis, emergence coronary artery bypass grafting, stroke, or cardiac arrest. Overall complications rate was 3.4% (3 patients). Minimum lumen diameter changed from 1.41 ± 0.46 mm to 3.53 ± 0.35 mm with an acute gain of 2.12 ± 0.49 mm. Mean residual stenosis was 9.4 ± 4.2% (Table 4).

Clinical follow-up was complete and all patients were followed for ≥12 months after the percutaneous procedure. Mean follow-up duration was 596 ± 230 days (range 365 to 826). No events occurred after discharge in the first 3 months of follow-up; at 6 months 1 patient developed an acute myocardial infarction (1.2%). In this patient angiogram documented that the infarct-related artery was the first obtuse marginal branch of the left circumflex artery with a de novo thrombotic occlusion. Target lesion revascularization was needed in 2 patients (2.4%), with in-segment restenosis localized at the ostium of the left circumflex artery in these patients. No death due to late angiographically adjudicated stent thrombosis occurred. At 12 months of follow-up, 1 cardiac death related to congestive heart failure

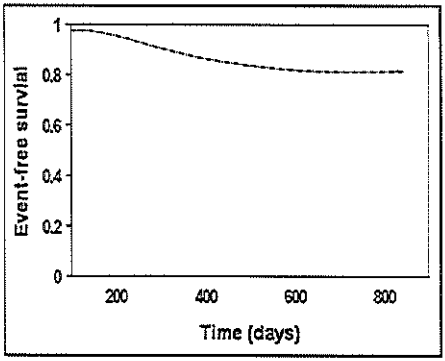


Figure 1. Event-free survival rate (88% and 82.3% at 1 and 2 years, respectively).

occurred. This patient had severe left ventricular dysfunction at the index procedure (left ventricular ejection fraction 32%), but postmortem autopsy was not performed.

During follow-up 3 other patients underwent target lesion revascularization within 12 months, and target lesion revascularization was needed in additional 2 patients ≥12 months after the index procedure. No late or very late thrombosis or myocardial infarction occurred in the remaining 65 patients. Event-free survival rates at 1 year and 2 years of follow-up were 88% and 82.3%, respectively (Figure 1).

Nine-month angiographic follow-up was performed in 71 patients (83%), whereas 13 patients declined angiographic control; these patients were without symptoms and events. Late lumen loss was 0.15 ± 0.81 mm, and overall binary angiographic restenosis rate was 9.8% (7 patients), with restenosis occurring in the mid LM artery in 1 patient and in the bifurcation lesions in the remaining 6. Four restenoses occurred in stents with a diameter <3.5 mm (all overexpanded with a 4.0-mm balloon during the index procedure). Moreover, occurrence of events during follow-up suggested an inverse association between risk and duration of follow-up, with 12 adverse events occurring in the first year of follow-up (66.7%), 5 occurring in the second year (27.8%), and only 1 occurring after the second year of follow-up (5.5%).

Incidence of angiographic and clinical outcomes in high-risk patients, diabetics, ejection fraction ≤35%, age >80 years, multivessel stenting, multivessel disease, previous myocardial infarction, previous percutaneous coronary intervention, bifurcation involvement, stent <3.5 mm, or postdilation with >3.5-mm balloons was similar to that of the overall population. Specifically, none of the subgroups was significantly associated with an increase in clinical or angiographic MACEs. However, patients treated "extremely" after dilation (thus achieving a final stent diameter 1 mm greater than the nominal stent size) showed a marginally significant increase ($p = 0.049$) in risk of clinical MACEs, likely due to a lack of large-diameter SESs in the beginning of our experience, which had to be overdilated to achieve adequate stent expansion and apposition.

Discussion

The present study suggests that use of drug-eluting stents to treat LM disease in unselected patients without major contraindications to cardiac surgery may be feasible, safe, and associated with a high procedural success rate. These findings are based on the lack, in our population, of episodes of stent thrombosis and on the very low incidence of procedure-related complications and in-hospital adverse events rate although many procedures were primary angioplasties for ST-elevation myocardial infarction. In addition, the safety of SES implantation in LM lesions is confirmed by the extremely low fatality observed. Early death occurred in only 1 patient classified as very high risk according to the EuroSCORE and the Parsonnet score who had a complex bifurcation lesion and died of cardiogenic shock during hospitalization.

Unprotected LM disease occurs in up to 5% of patients undergoing coronary angiography, with as many as 50% also having associated 3-vessel coronary disease and/or co-morbidities that pose a high risk for any type of invasive procedure. Although coronary artery bypass grafting has been the treatment of choice of LM disease for decades,[12] percutaneous revascularization had been attempted for LM disease in the balloon-only and bare metal stent eras, with suboptimal results.[13,14] Percutaneous revascularization for LM disease may carry a potential risk of early and late failures, and these findings led to evidence-based recommendations restricting percutaneous revascularization for LM disease only to patients with prohibitive surgical risk.[15]

Since market approval of SESs, several interventionists have employed these devices not only in patients with LM disease at very high surgical risk (e.g., acute ST-elevation myocardial infarction) but also in those with more favorable anatomy and/or clinical characteristics.[1] Although preliminary data from high-volume centers, including comparisons between drug-eluting stents and surgery,[16–18] have provided promising results for early and midterm rates of MACEs in patients with unprotected LM disease treated with drug-eluting stent implantation (with midterm MACEs and target vessel revascularization as low as 5.8% and 1.9%, respectively),[19] all reports published to date were relatively small and lacked long-term follow-up.[16,20,21] The latter feature is a major limitation of the available evidence base, especially because of recent data suggesting a potential long-term hazard with drug-eluting stents.[3,22]

Late follow-up confirms that the risk of events after LM stenting with drug-eluting stents progressively decreases over time, even if some attrition persists.[23] Further, the rate of binary angiographic restenosis was relatively low and all but 1 restenotic lesion was focal and treatable with reintervention. Although such a restenosis rate appears lower than those with bare metal stents, a rate of 10% with SES could still be clinically dis-satisfying compared with the patency of bypass grafts (especially in the left internal mammary artery).[18] Moreover, our data based on selective use of a 2-stent approach indicate that it is feasible, safe, and likely less associated with thrombosis than a systematic 2-stent strategy.[7,8]

In our study some patients received 3.0-mm SESs because the 3.5-mm SESs were not available at the beginning of enrollment. In these patients stents were overexpanded with oversized noncompliant balloons (≥3.5 mm diameter). Such a stent after dilation with an oversized balloon (balloon/stent ratio >1.2) was the predictor of MACEs at follow-up. Although previous studies seemed to support such

a practice,[24] this risk was particularly magnified for stents expanded to a final diameter >1 mm than their nominal size, suggesting that extreme stent overexpansion may lead to strut fracture, polymer damage, irregular drug elution, and/or suboptimal plaque scaffolding.

Drawbacks of this work are those typical of single-center observational studies with a relatively small sample.[25] Given the lack of large studies on SES implantation for LM disease and especially of any study reporting on long-term outcomes, this study, despite its inherent limitations in internal and external validities, adds important information about the use of SESs in this patient subset.

Despite our promising results, the importance of patient selection and multidisciplinary approach (involving a noninvasive cardiologist and a cardiac surgeon) seems pivotal to identifying those patients with LM disease more likely to benefit from drug-eluting stents and less likely to be harmed by it.[26]

1. Huang HW, Brent BN, Shaw RE. Trends in percutaneous versus surgical revascularization of unprotected left main coronary stenosis in the drug-eluting stent era—a report from the American College of Cardiology–National Cardiovascular data registry (ACC-NCDR). *Catheter Cardiovasc Interv* 2006;68:867–872.
2. Sheiban I, Meliga E, Moretti C, Fumagalli A, Omedè P, Sciuto F, Grossomarra W, Trevi G. Sirolimus-eluting stents vs bare metal stents for the treatment of unprotected left main coronary artery stenosis. *EuroInterv* 2006;2:356–362.
3. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. *Eur Heart J* 2006;27:2784–2814.
4. Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. *Circulation* 1989;79(suppl I):I3–I12.
5. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999;16:9–13.
6. Biondi-Zoccai GG, Agostoni P, Sangiorgi GM, Airoldi F, Cosgrave J, Chieffo A, Barbagallo R, Tamburino C, Vittori G, Falchetti E, et al, for the Real-world Eluting-stent Comparative Italian retrosPective Evaluation Study Investigators. Incidence, predictors, and outcomes of coronary dissections left untreated after drug-eluting stent implantation. *Eur Heart J* 2006;27:540–546.
7. Steigen TK, Maeng M, Wiseth R, Erglis A, Kumsars I, Narbute I, Gunnes P, Mannsverk J, Meyerdierks O, Rotevatn S, et al, for the Nordic PCI Study Group. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. *Circulation* 2006;114:1955–1961.
8. Ge L, Airoldi F, Iakovou I, Cosgrave J, Michev I, Sangiorgi GM, Montorfano M, Chieffo A, Carlino M, Corvaja N, Colombo A. Clinical and angiographic outcome after implantation of drug-eluting stents in bifurcation lesions with the crush stent technique: Importance of final kissing balloon post-dilation. *J Am Coll Cardiol* 2005;46:613–620.
9. Agostoni P, Valgimigli M, Abbate A, Cosgrave J, Pilati M, Biondi-Zoccai GG. Is late luminal loss an accurate predictor of the clinical effectiveness of drug-eluting stents in the coronary arteries? *Am J Cardiol* 2006;97:603–605.
10. Cosgrave J, Melzi G, Biondi-Zoccai GG, Airoldi F, Chieffo A, Sangiorgi GM, Montorfano M, Michev I, Carlino M, Bonizzoni E, Colombo A. Drug-eluting stent restenosis the pattern predicts the outcome. *J Am Coll Cardiol* 2006;47:2399–2404.
11. Biondi-Zoccai GG, Sangiorgi GM, Chieffo A, Vittori G, Falchetti E, Margheri M, Barbagallo R, Tamburino C, Remigi E, Briguori C, et al, for the RECIPE (Real-world Eluting-stent Comparative Italian retrosPective Evaluation) Study Investigators. Validation of predictors of intraprocedural stent thrombosis in the drug-eluting stent era. *Am J Cardiol* 2005;95:1466–1468.
12. Chaitman BR, Fisher LD, Bourassa MG, Davis K, Rogers WJ, Maynard C, Tyras DH, Berger RL, Judkins MP, Ringqvist I, Mock MB, Killip T. Effect of coronary bypass surgery on survival patterns in subsets of patients with left main coronary artery disease. Report of the Collaborative Study in Coronary Artery Surgery (CASS). *Am J Cardiol* 1981;48:765–777.
13. O'Keefe JH Jr, Hartzler GO, Rutherford BD, McConahay DR, Johnson WL, Giorgi LV, Ligon RW. Left main coronary angioplasty: early and late results of 127 acute and elective procedures. *Am J Cardiol* 1989;64:144–147.
14. Takagi T, Stankovic G, Finci L, Toutouzas K, Chieffo A, Spanos V, Liistro F, Briguori C, Corvaja N, Albero R, et al. Results and long-term predictors of adverse clinical events after elective percutaneous interventions on unprotected left main coronary artery. *Circulation* 2002;106:698–702.
15. Silber S, Albertsson P, Aviles FF, Camici PG, Colombo A, Hamm C, Jorgensen E, Marco J, Nordrehaug JE, Ruzyllo W, et al, for the Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J* 2005;26:804–847.
16. Chieffo A, Morici N, Malsano F, Bonizzoni E, Cosgrave J, Montorfano M, Airoldi F, Carlino M, Michev I, Melzi G, et al. Percutaneous treatment with drug-eluting stent implantation versus bypass surgery for unprotected left main stenosis. A single-center experience. *Circulation* 2006;113:2542–2547.
17. Lee MS, Kapoor N, Jamal F, Czer L, Aragon J, Forrester J, Kar S, Dohad S, Kass R, Eigler N, et al. Comparison of coronary artery bypass surgery with percutaneous coronary intervention with drug-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol* 2006;47:864–870.
18. Palmerini T, Marzocchi A, Marrozzini C, Ortolani P, Saia F, Savini C, Bacchi-Reggiani L, Gianstefani S, Virzi S, Manara F, et al. Comparison between coronary angioplasty and coronary artery bypass surgery for the treatment of unprotected left main coronary artery stenosis (the Bologna Registry). *Am J Cardiol* 2006;98:54–59.
19. de Lezo JS, Medina A, Pan M, Delgado A, Segura J, Pavlovic D, Melian F, Romero M, Burgos L, Hernandez E, Urena I, Herrador J. Rapamycin-eluting stents for the treatment of unprotected left main coronary disease. *Am Heart J* 2004;148:481–485.
20. Agostoni P, Valgimigli M, Van Mieghem CA, Rodriguez-Granillo GA, Aoki J, Ong AT, Tsuchida K, McFadden EP, Ligthart JM, Smits PC, et al. Comparison of early outcome of percutaneous coronary intervention for unprotected left main coronary artery disease in the drug-eluting stent era with versus without intravascular ultrasonic guidance. *Am J Cardiol* 2005;95:644–647.
21. Valgimigli M, Malagutti P, Aoki J, Garcia-Garcia HM, Rodriguez Granillo GA, van Mieghem CA, Ligthart JM, Ong AT, Sianos G, Regar E, et al. Sirolimus-eluting versus paclitaxel-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: a combined RESEARCH and T-SEARCH long-term analysis. *J Am Coll Cardiol* 2006;47:507–514.
22. Bavry AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. *Am J Med* 2006;119:1056–1061.
23. Valgimigli M, Malagutti P, van Mieghem CA, Vaina S, Ligthart JM, Sianos G, Serruys PW. Persistence of neointimal growth 12 months after intervention and occurrence of delayed restenosis in patients with left main coronary artery disease treated with drug-eluting stents. *J Am Coll Cardiol* 2006;47:1491–1494.
24. Iakovou I, Stankovic G, Montorfano M, Airoldi F, Chieffo A, Sangiorgi GM, Carlino M, Corvaja N, Iassen M, Rogacka R, Vitrella G, Colombo A. Is overdilatation of 3.0 mm sirolimus-eluting stent associated with a higher restenosis rate? *Catheter Cardiovasc Interv* 2005;64:129–133.
25. Biondi-Zoccai GG, Agostoni P, Abbate A. Parallel hierarchy of scientific studies in cardiovascular medicine. *Ital Heart J* 2003;4:819–820.
26. Hodgson JM, Stone GW, Lincoff AM, Klein L, Walpole H, Bottner R, Weiner BH, Leon MB, Feldman T, Babb J, Dehmer GJ. Late stent thrombosis: considerations and practical advice for the use of drug-eluting stents: a report from the Society for Cardiovascular Angiography and Interventions drug-eluting stent task force. *Catheter Cardiovasc Interv* 2007;69:327–333.

CHAPTER 7

SIROLIMUS-ELUTING STENTS VS BARE METAL STENTS FOR THE TREATMENT OF UNPROTECTED LEFT MAIN CORONARY ARTERY STENOSIS

Clinical research

EuroIntervention

Sirolimus-Eluting Stents vs Bare Metal Stents for the treatment of unprotected left main coronary artery stenosis

Imad Sheiban*, Emanuele Meliga, Claudio Moretti, Alison Fumagalli, Pierluigi Omedè, Filippo Sciuto, Walter Grossomarra, Gianpaolo Trevi

Interventional Cardiology, Division of Cardiology, University of Torino, San Giovanni Battista Hospital, Torino, Italy

The authors have no conflict of interest to declare.

KEYWORDS
Left main coronary artery, coronary angioplasty, drug-eluting stents, bare metal stents, coronary artery disease

Abstract

Aim: This study compares the clinical and angiographic outcomes of sirolimus eluting stent (SES) and bare metal stent (BMS) implantation for unprotected left main coronary artery (ULMCA) stenosis.

Methods and results: We analysed 141 unselected patients with unprotected LMCA stenosis: 72 were treated with SES and 69 with BMS. SES patients were younger, with a higher ejection fraction, had more often hypertension, family history and were more often smokers. The procedural success rate was 94.2% in SES group and 87% in BMS group. In SES group there were 2 periprocedural myocardial infarction (3%). 1 intra-procedural death (1.4%) and 1 in-hospital death (1.4%) and respectively 2 (3%),4 (6%) and 3 (4%) in BMS group. No incidents of stent thrombosis, stroke and emergent CABG occurred during hospitalisation in either group. SES patients showed a lower late lumen loss (0.5±0.8 mm vs 1.1±1.0 mm; p<0.05) and a lower nine-month angiographic restenosis rate (13.6% vs 24.3%; p=NS). The MACE free survival rate at 2 years was 83% in the SES group vs 55% in the BMS group (p<0.001).

Conclusions: SES implantation for unprotected LMCA stenosis in "real world" population appears safe with a low restenosis and MACE rate at follow-up.

* *Corresponding author: Interventional Cardiology, Division of Cardiology, University of Torino, San Giovanni Hospital, Corso Bramante 88-90, 10126 Torino, Italy*
E-mail: isheiban@yahoo.com

Introduction

Lesions in the LM are still considered a standard indication for surgical revascularisation[1-3], unless several studies have demonstrated the safety and feasibility of unprotected LMCA intervention using BMS[4-22]. In effect the main limit of this approach is the in-stent restenosis (ISR), often associated with an increase of long-term mortality[19]. Recently, several studies and reports suggest that use of DES has been associated with a lower restenosis rate and with favourable clinical outcomes even though these studies included small number of patients and low rates of angiographic follow up[23-29]. The aim of the present study is to provide a further contribution in this controversial field reporting the clinical and angiographic outcomes of the use of SES in the treatment of unprotected LMCA stenosis and comparing the results with those of BMS in the same patients subset.

Methods

Study population

From July 2002 to December 2004, 72 consecutive patients who were admitted to the Interventional Cardiology Laboratory underwent percutaneous coronary intervention (PCI) procedures with SES implantation for critical unprotected LMCA disease. The control group consisted of 69 consecutive patients selected from December 2000 to December 2004 with similar angiographic findings and treated with BMS implantation.

PCI procedure was performed when a suitable anatomy for stenting was present, associated with symptomatic LMCA disease or documented myocardial ischaemia. Patients with contraindication for double anti-aggregation or anticoagulation therapy were excluded. The informed consent was obtained in accordance with the Declaration of Helsinki.

For every patient, we evaluated the following baseline parameters: cardiovascular risk factors (age, sex, hypertension, diabetes, hyperlipidaemia, family history for coronary artery disease [CAD] and cigarette smoking), presence of prior myocardial infarction, previous coronary artery bypass graft (CABG) or PTCA, presence of specific comorbidity (such as chronic renal failure and peripheral vasculopathy), clinical presentation (ST Elevation Myocardial Infarction, or STEMI; Non ST Elevation Myocardial Infarction, or NSTEMI; unstable angina, or UA; stable angina; ventricular arrhythmias; acute pulmonary oedema, or APE; or instrument signs of ischaemia), angiographic pattern (extension of CAD, lesion location and quantitative coronary angiography, or QCA, evaluation).

The patients were also stratified in risk classes using both Parsonnet score system and EuroSCORE (European system for cardiac operative evaluation).

Procedural characteristics included the following parameters: treatment of distal LMCA bifurcation with single or double stent; the utilisation of final kissing balloon for bifurcation lesions, debulking procedure (directional or rotational atherectomy), pressure wire or intra-vascular ultrasound (IVUS) guided revascularisations and use of intra-aortic balloon pump (IABP). Creatine kinase (CK) measurements were systematically performed on admission and every 3 hr. for the subsequent 24 hr., and then every 12 hr. for 2 days. The peak value of CK-MB and T troponin were estimated for each patient. Aspirin was administered to all patients before the procedure and indefinitely thereafter. A loading dose of clopidogrel was performed at least 4 hours before the catheterisation and the double anti-aggregation therapy (aspirin + clopidogrel or aspirin + ticlopidine) continued for at least 6 months. Glycoprotein IIb/IIIa inhibitor use was at the discretion of the operator.

Stenting procedure

In general, predilation was performed only in very tight lesions using undersized conventional balloons. In calcified lesions, a matched balloon to vessel size (1:1) was used. The stent deployment was achieved by inflating the delivery balloon at nominal pressure. In selected cases, the stented segment was then further dilated with high pressure balloon inflations, to achieve the optimal diameter. All the lesions has been fully covered; lesions involving ostium or shaft without involvement of bifurcation were treated with a single stent. Lesions involving bifurcation were treated as follows: stenting across left circumflex artery (LCX)-ostium, stenting across left anterior descending-LAD-ostium, kissing stenting and provisional T-stenting. No lesion was treated with crushing or culotte technique. Final kissing balloon dilation was performed in almost all patients. IVUS guidance was used in those lesions with a not completely convincing final angiographic aspect.

Quantitative coronary angiography (QCA) analysis

Using a semi-automated dedicated software (Inturis viewer package software 1.2 version, Philips), all the angiograms were analysed at baseline, after procedure and at follow-up, measuring minimal lumen diameter (MLD), percent diameter stenosis, reference vessel diameter (RVD), lesion length, acute gain and late lumen loss. The reference diameter has been obtained as average diameter of proximal and distal normal segments or in contiguous normal segments in case of ostial and bifurcation lesions.

Follow-up

The follow-up ended for all patients on the 30th April 2005; the mean follow-up period for the whole population was 23.6±12 months (18±8 months in SES group; 29±10 months in BMS group). Periodical phone interviews and office visits were scheduled at 1, 3, 6 and 12 months and at the end of the follow-up period (April 2005). A coronary angiography was routinely performed after 9 months, or earlier if driven by clinical symptoms or documented myocardial ischaemia.

Definition

Procedural success was defined as revascularisation with a residual stenosis <30% at the QCA, without major intraprocedural or in-hospital adverse events (acute myocardial infarction, or AMI; death or emergent CABG).

Deaths were divided into cardiac and non cardiac; those that were not surely classifiable were considered as cardiac.

Major adverse cardiac events (MACEs) were defined as the occurrence of death, non-fatal MI, stroke and TLR/TVR.

Target lesion revascularisation (TLR) was defined as any revascularisation on the treated segment.
Target vessel revascularisation (TVR) was defined as any revascularisation on the treated vessel.
STEMI was defined as increase of Ck-MB 3 times over the upper limit of normal together with typical ST elevation at the ECG control.
NSTEMI was defined as increase of Ck-MB 3 times over the upper limit of normal without ST elevation at the ECG control.
Restenosis was defined as lumen reduction at the segment site (i.e. stent length plus 5 mm proximally and distally) >50% at the QCA.
High risk patients had Parsonnet >15 and EuroSCORE > 6. Very high risk patients had Parsonnet >20 and EuroSCORE > 13.

Statistical analysis

Univariate analysis was performed to evaluate baseline clinical and angiographic differences in the two groups; multivariate analysis was performed to evaluate correlations between baseline clinical and procedural parameters and the recurrence of intra-hospital adverse events or MACEs during the follow-up. Data are expressed as mean±SD for continuous variables and as frequencies for categorical variables.
Difference between group were evaluated using chi-square and Student-T test. MACE-free survival distributions were assessed according to the Kaplan Meier method. To compare MACE-free survival between the two groups we used the Log-Rank test. All the analysis were performed using dedicated software (SAS and Statistica).

Results

Patients and lesion characteristics

The baseline clinical and angiographic characteristics are summarised in Tables 1 and 2. At the univariate analysis patients treated with SES compared to BMS group were younger (68% vs 73.6%; p< 0.05), had a higher ejection fraction, or EF (55.2% vs 46%; p<0.05), had more hypertension (85% vs 57%; p< 0.05), family history (24% vs 10%; p< 0.05), were more often current smokers (24% vs 6%; p<0.05), were more often treated with statins (44% vs 19%; p<0.05); patients treated with BMS more often presented with NSTEMI (25% BMS, 7% SES; p<0.05) and distal lesion location was significantly higher in BMS group (58% in SES group vs.70% in BMS group; p<0.05) compared to SES group.

Procedural results

Procedural characteristics are shown in Table 3. Compared to the group treated with BMS, the SES group needed less IABP (8% vs 20%; p<0.05) and received more often post-dilatation (65% vs 30%; p<0.05). Final kissing balloon dilation was performed in almost all patients with no difference in two groups (90% DES group, 88% BMS). IVUS guidance was used in both groups with no significant difference (DES group n= 8-11%; BMS group n=3- 4%). The procedural success rate was 94.2% in SES group and 87% in BMS group. Table 4 shows intra-procedural and in-hospital adverse events. Periprocedural MI occurred in 2 patients (3%) in SES group and 2 patients (3%) in BMS group (p=NS); intra-procedural death occurred in 1 patient (1.4%) in SES group and in 4 patients (6%) in BMS group (Table 5). In-hospital death occurred in 1 patient (1.4%) in SES group and in 3 patients (4%) in BMS group (Table 5). No incidents of subacute stent thrombosis, stroke and emergent CABG occurred. Total in-hospital adverse events rate was 5.8% in SES group versus 13% in BMS group.

Table 1. Baseline clinical characteristics

	SES(n=72)		BMS(n=69)		P value
	Total (%)	Mean (SD)	Total (%)	Mean (SD)	
Age		68(10)		73.6(11.8)	<0.05
Men	56(77)		48(69)		NS
Hypertension	61(85)		39(57)		<0.05
Diabetes (NIDDM and IDDM)	16(22)		14(20)		NS
IDDM	8(11)		6(9)		NS
Current smokers	17(24)		4(6)		<0.05
Family history	17(24)		7(10)		<0.05
Hypercholesterolaemia	42(58)		31(45)		NS
Use of statins	32(44)		13(19)		<0.05
Chronic renal failure	3(4)		8(12)		NS
Peripheral vasculopathy	17(24)		17(25)		NS
Known coronary Artery Disease (CAD)	34(47)		38(55)		NS
Previous AMI	21(29)		29(42)		NS
Previous CABG	14(19)		10(14)		NS
Previous PCI	20(28)		15(22)		NS
Mean Ejection Fraction		55.2(10.3)		46.0(12.9)	<0.05
Acute pulmonary oedema	1(1)		1(1)		NS
STEMI	9(13)		4(6)		NS
NSTEMI	5(7)		17(25)		<0.05
Unstable angina	34(47)		32(46)		NS
Stable angina	9(13)		2(3)		NS
Documented ischaemia	9(13)		12(17)		NS
Others	5(7)		1(1)		NS

SES= Sirolimus Eluting Stent group; BMS= Bare Metal Stent group; SD= standard deviation; NS= not significant

Follow-up results

Nine months angiographic follow-up was performed on 44 patients (61%) of SES group and on 37 patients (54%) of BMS group. Event driven angiography was performed on 12 SES patients (28%) and on 7 BMS patients (19%). The QCA results are summarised in Table 2. Late lumen loss was significantly lower in the SES group (0.5±0.8 mm vs. 1.1±1 mm; p<0.05) than BMS group; the angiographic restenosis rate was lower as well, even though p value was not statistically significant (13.6% vs 24.3%; p=NS).
In the SES group restenosis occurred in 7 patients; 71% of restenosis (n=5) occurred in patients with bifurcation LMCA lesions; all the re-stenosis, except one, were found out at the nine-month angiographic control in asymptomatic patients; restenosis were all focal, except one, and all were successfully treated with a new SES implantation (Table 6).

Table 2. Baseline angiographic characteristics.

	SES(n=72)		BMS(n=69)		P value
	Total (%)	Mean (SD)	Total (%)	Mean (SD)	
INDEX PROCEDURE					
Baseline QCA	72(100)		69(100)		
Final QCA	72(100)		69(100)		
Baseline minimal lumen Diameter,mm		1.4(0.5)		1.6(0.4)	NS
Final minimal lumen diameter, mm		3.5(0.3)		3.8(0.3)	NS
Baseline diameter stenosis,%		62(12.3)		59.8(9.5)	NS
Final diameter stenosis,%		9.5(4.2)		7.2(4.6)	NS
Baseline reference diameter, mm		3.7(0.4)		4.0(0.3)	NS
Final reference diameter, mm		3.9(0.3)		4.1(0.4)	NS
Lesion length, mm		20(19)		22.1(16.2)	NS
Stent diameter, mm		3.2(0.28)		3.5(0.3)	NS
Ostium	25(35)		21(30)		NS
Shaft	19(26)		17(25)		NS
Bifurcation	42(58)		48(70)		<0.05
9 MONTHS ANGIO-CONTROL					
Baseline QCA	44(61)		37(54)		
Final QCA (restenosis)	6(8)		9(13)		
Baseline minimal lumen diameter, mm		3(0.8)		2.9(1.1)	NS
Final minimal lumen diameter, mm		3.3(0.6)		3.5(0.6)	NS
Baseline diameter stenosis, %		18.9(22.4)		25(24.8)	NS
Final diameter stenosis, %		14.2(9.8)		11.3(10.8)	NS
Baseline reference diameter, mm		3.8(0.6)		4(0.8)	NS
Final reference diameter, mm		3.8(0.5)		3.9(0.3)	NS
Lesion length, mm		4.4(1.3)		4.1(1.4)	NS
Late lumen loss		0.5(0.8)		1.1(1)	<0.05
Acute gain		2.1(0.5)		2.2(0.5)	NS

SES= Sirolimus Eluting Stent group; BMS= Bare Metal Stent group; SD= standard deviation; NS= not significant

Table 3. Baseline procedural characteristics.

	SES(n=72)		BMS(n=69)		P value
	Total (%)	Mean (SD)	Total (%)	Mean (SD)	
Double stent	24(33)		25(36)		NS
Single stent	18(25)		23(33)		NS
Stents per patient		1.38(0.6)		1.59(0.78)	NS
Use of additional high-pressure balloon	47(65)		21(30)		<0.05
Maximal balloon size,mm		3.8(0.2)		4(0.4)	
Maximal inflation pressure, atm		18.9(2.9)		17.8(3.4)	
Multivessel involvement	63(88)		66(96)		NS
Primary PCI	5(7)		8(12)		NS
Rescue PCI	0(0)		0(0)		NS
Multivessel treatment	58(81)		63(91)		NS
2 vessels	35(49)		40(58)		
3 vessels	23(32)		23(33)		
Use of glycoprotein 2b/3a inhibitors	25(35)		21(30)		NS
Directional coronary atherectomy (DCA)	2(3)		2(3)		NS
Rotablator	1(1)		0(0)		NS
Kissing balloon predilatation	21(29)		16(23)		NS
Guidance of intravascular ultrasound (IVUS)	8(11)		3(4)		NS
Support of intra-aortic balloon pump (IABP)	6(8)		14(20)		<0.05

SES= Sirolimus Eluting Stent group; BMS= Bare Metal Stent group; SD= standard deviation; NS= not significant

Table 4. Intra-procedural and in-hospital adverse events.

	SES(n=72) Total(%)	BMS(n=69) Total(%)	P value
Periprocedural MI (non Q)	2(3)	2(3)	NS
Intraprocedural death	1(1.4)	4(6)	NS
Intrahospital death	1(1.4)	3(4)	NS
Acute stent thrombosis	0(0)	0(0)	NS
Emergent CABG	0(0)	0(0)	NS
Stroke	0(0)	0(0)	NS
Total	4(5.8)	9(13)	NS

SES= Sirolimus Eluting Stent group; BMS= Bare Metal Stent group; NS= not significant

Table 5. Intraprocedural and in-hospital deaths in SES and BMS group.

	Age	EF	Multivessel involvement	Clinical manifestation	Parsonnet	EuroSCORE	Cause of death
SES							
1 IP	64	45	Yes	Cardiac arrest	20	15.12	Cardiogenic shock
2 IH	43	54	Yes	Cardiogenic shock	18	16.13	MOF
BMS							
1 IP	73	35	Yes	Cardiogenic shock	15	10.44	Cardiogenic shock
2 IP	80	60	No	Stemi	20	9.28	Cardiogenic shock
3 IP	83	55	Yes	Unstable angina	25	14.11	PEA
4 IP	64	35	Yes	Nstemi	70	50.72	PEA
5 IH	66	45	Yes	Nstemi	45	24.7	Cardiogenic shock
6 IH	90	40	Yes	Nstemi	72	35.97	Sudden death
7 IH	73	25	Yes	Unstable angina	12	10.64	MOF

IP = intraprocedural event; IH = intrahospital event; EF= ejection fraction; MOF= multi organ failure; PEA= pulseless electrical activity

Table 6. Patients of the SES group with angiographic restenosis.

Age, Gender	Lesion Location	Restenosis pattern	Procedure
76,M	ostium	focal	repeat SES stenting
73,M	bifurcation	focal	repeat SES stenting
69,F	bifurcation	focal	repeat SES stenting
77,M	bifurcation	focal	POBA
68,M	bifurcation	focal	repeat SES stenting
53,M	bifurcation	focal	repeat SES stenting
69,M	ostium	diffuse	repeat SES stenting

M = male; F = female

In the BMS group restenosis occurred in 13 patients and all were in patients with bifurcation LMCA lesions; 5 patients underwent angiographic control for recurrence of angina and 8 were scheduled angiographic controls; restenosis were focal in 4 patients while in 9 were diffuse. All except one (sent to CABG) were successfully treated with SES implantation.

Clinical follow-up information was collected in 100% of the patients in the SES group and 99% in the BMS group. The mean clinical follow-up duration was 18±8 months in SES group; 29±10 months in BMS group. Target lesion revascularisation at one year was performed in 6 SES patients and in 9 BMS patients (13.6% vs 24.3%, P=NS). No deaths or acute MIs occurred in either group. The MACE free survival rate at 2 years was 83% in the SES group vs 55% in the BMS group (p<0.001); see Figure 1 (Kaplan-Meier curves for two-years MACE-free survival in patients treated with SES and BMS. A statistically significant difference was observed between the two groups - log rank=0.00131. MACE = major adverse cardiac events including death, non-fatal myocardial infarction, stroke and TLR/TVR).

At the multivariate analysis the only variable related with a significant reduction of MACE was the use of SES (p=0.0024); on the other side, variable significantly related with an increased MACE incidence was the presence of bifurcation lesion (p=0.025).

Patients over 75 years, diabetics, with a poor EF (<35%) and High risk patients (EuroSCORE>6 and Parsonnet >15) had a slightly higher MACE incidence, though p value was not statistically significant in both groups (p=0.16 and p=0.09).

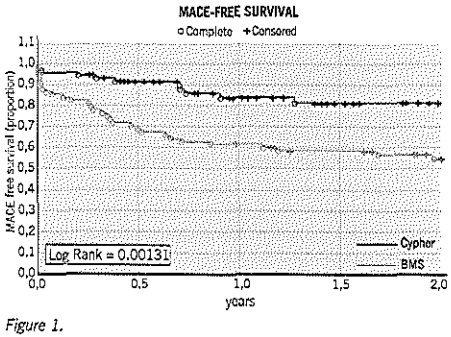


Figure 1.

Discussion

The findings of the present study show that in patients with coronary artery disease, SES implantation for the treatment of unprotected LMCA lesions is feasible and safe. In fact, it is associated with a low procedure-related complication rate and without subacute or late stent thrombosis. Compared to SES, BMS implantation is associated with a higher intra-procedural complication rate. This might be due to the fact that patients treated with BMS were elder and with lower ejection fraction. Long-term clinical outcome was also better in patients treated with SES likely due to the reduction of in-stent restenosis with the use of SES (13.6% vs 24.3%; p=NS).

In contrast with prior studies[24,28] that included a large number of elective patients, this one can be considered a "real world" study: the population of the study were consecutive "all comers" patients including those with poor EF, with "very high risk" profile (EuroSCORE>13 and Parsonnet> 20), diabetics and patients who underwent primary percutaneous coronary intervention (PCI) for acute coronary syndromes (AMI or UA). This might explain the slightly lower procedural success rates of this study compared to previous studies and for this reason the results obtained in this study might be considered excellent, despite the high risk profile of our population. High-risk sub-groups indeed don't move away significantly from the whole population in terms of incidence of MACE. The only negative predictor of MACE seems to be the presence of distal LMCA bifurcation lesion, though the rate of lesions involving bifurcation is significantly different in the two groups (58% in SES group vs. 70% in BMS group; p<0.05).

LMCA bifurcation lesions are still considered infeasible for percutaneous intervention both for the technical difficulties of stenting and the higher incidence of in-stent restenosis involving the large side branches (especially left circumflex artery). Several studies comparing the use of SES with historical controls[32-34] for the treatment of LMCA bifurcation lesions, showed a very low restenosis rate in the main vessel and no benefit in terms of reduction of restenosis of side branch with the use of SES for both bifurcation branches (two stents) over single stent and balloon angioplasty for the second branch (provisional T stenting). Moreover, no superiority of single technique (T Stenting vs Coulotte vs Crush) has ever been demonstrated.

Thus, even in the era of the drug eluting stent the higher overall restenosis rate in bifurcation lesions remains a challenge. However the compelling results of this study and others[32-34] showing very low rates of restenosis and TLR indicate that the treatment of LMCA bifurcation may become an achievable goal for PCI with SES. Clinical follow-up demonstrated that the use of SES significantly reduces the incidence of MACE; the event-free survival at 2 year was 83% in SES group vs 55% in BMS group (log rank = 0.00131), corresponding to a 62.3% relative reduction of risk; moreover, the use of SES was related with a 93.7% relative reduction in all cause death (survival at 2 years: 98% SES vs 68% BMS; log-rank = 0.00009) and with a 91% relative reduction in cardiovascular death (survival at 2 years: 98% SES vs 78% BMS; log rank = 0.00119). These results suggest that the use of SES is associated both with a better quality of life due to a reduction in event driven hospitalisations and with a lower incidence of cardiovascular death.

It is indeed well known that in-stent restenosis leads more often to repeat interventions (PCI or surgery) and also might influence long term survival because might cause sudden death. SES has been shown to be very effective in suppressing intimal growth even in complex LMCA lesions (as documented also in the present study) reducing long term in-stent restenosis which is consequently translated by better long-term clinical outcomes.

While prior studies have demonstrated safety and efficacy of DES implantation on a relatively short-term period[30,31], this study has prolonged the mean observational period up to 2 years, providing important confirmation of sustained safety and effectiveness of SES implantation for unprotected LMCA stenosis.

The major limitation of the present study is represented by the fact that some differences can be found in the baseline clinical and lesion characteristics between the two groups; patients belonging to BMS group are older, with a lower LVEF, more often presented with NSTEMI and more frequently were affected by distal LM stenosis. This means that the poorer outcome of BMS group might have been influenced by the higher risk profile of BMS patients and therefore that the superiority of DES shown in this paper could be less evident if the two groups were right balanced. Moreover these findings are based on a single centre observational study and that the number of patients is relatively small to generalise our results to all patients with LMCA lesions. Data deriving from long term and multicentre randomised study comparing SES implantation and bypass surgery are needed and will help us to clarify better the potentiality and the role of this approach.

Conclusions

The use of BMS for the treatment of ULMCA lesions is associated with a high events rate both in hospital and during FU period. On the other hand, SES implantation for the treatment of the same lesion subset in a "real world" population is safe and effective, with a very low procedure-related complication rate and with an extremely encouraging 2 years MACE free survival (83%) both for low risk patients and for high risk sub-groups.

Based on these findings and those already reported in literature, PCI for ULMCA with SES implantation should be suggested.

References

1. Takaro T, Peduzzi P, Detre KM, Hultgren HN, Murphy ML, van der Bel-Kahn J, Thomsen J, Meadows WR. Survival in subsets of patients with left main coronary artery disease. Veterans Administration Cooperative study of surgery for coronary arterial occlusive disease. *Circulation* 1982;66:14-22.

2. Caracciolo EA, Davis KB, Sopko G, Kaiser GC, Corley SD, Schaff H, Taylor HA, Chaitman BR. Comparison of surgical and medical group survival in patients with left main coronary artery disease: long-term CASS experience. *Circulation* 1995;91:2325-2334.

3. D'Allonnes FR, Corbineau H, Le Breton H, Leclercq C, Leguerrier A, Daubert C. Isolated left main coronary artery stenosis: long term follow up in 106 patients after surgery. *Heart* 2002;87:544 -548.

4. Detre KM, Wright E, Murphy ML, Takaro T. Observer agreement in evaluating coronary anglograms. *Circulation* 1975;52:979-86.

5. Gazetopoulos N, Ioannidis PJ, Karydis C, Lolas C, Kiriakou K, Tountas C. Short left coronary artery trunk as a risk factor in the development of coronary atherosclerosis. Pathological study. *Br Heart J* 1976;38:1160-65.

6. Sanmarco ME, Brooks SH, Blankenhorn DH. Reproducibility of a consensus panel in the interpretation of coronary angiograms. Am Heart J. 1978;96:430-437.

7. Isner JM, Kishel J, Kent KM, Ronan JA Jr, Ross AM, Roberts WC. Accuracy of angiographic determination of left main coronary arterial narrowing: angiographic-histologic correlative analysis in 28 patients. *Circulation* 1981;63:1056-64.

8. Fisher LD, Judkins MP, Lesperance J, Cameron A, Swaye P, Ryan T, Maynard C, Bourassa M, Kennedy JW, Gosselin A, Kemp H, Faxon D, Wexler L, Davis KB. Reproducibility of coronary arteriographic reading in the Coronary Artery Surgery Study (CASS). *Cathet Cardiovasc Diagn* 1982;8:565-575.

9. Cameron A, Kemp HG Jr, Fisher LD, Gosselin A, Judkins MP, Kennedy JW, Lesperance J, Mudd JG, Ryan TJ, Silverman JF, Tristani F, Vlietstra RE, Wexler LF. Left main coronary artery stenosis: angiographic determination. *Circulation* 1983;68:484-489.

10. Asakura T, Karino T. Flow patterns and spatial distribution of atherosclerotic lesions in human coronary arteries. *Circ Res* 1990;66:1045-1066.

11. Flemming RM, Kirkeelde RL, Smalling RW, Gould KL. Patterns in visual interpretation of coronary arteriograms as detected by quantitative coronary arteriography. *J Am Coll Cardiol* 1991;18:945-51.

12. Herrmiller JB, Buller CE, Tenaglia AN, Kisslo KB, Phillips HR, Bashore TM, Stack RS, Davidson CJ. Unrecognised left main coronary artery disease in patients undergoing interventional procedures. *Am J Cardiol* 1993;71:173- 6.

13. Abizaid AS, Mintz GS, Abizaid A, Mehran R, Lansky AJ, Pichard AD, Satler LF, Wu H, Kent KM, Leon MB. One year follow-up after intravascular ultrasound assessment of moderate left main coronary artery disease in patients with ambiguous angiograms. *J Am Coll Cardiol* 1999;34:707.

14. Silvestri M, Barragan P, Sainsous J, Bayet G, Simeoni JB, Roquebert PO, Macaluso G, Bouvier JL, Comet B. Unprotected left main coronary artery stenting: immediate and medium long term outcomes of 140 elective procedures. *J Am Coll Cardiol* 2000;35: 1543.

15. Maehara A, Mintz GS, Castagna MT, Pichard AD, Satler LF, Waksman R, Laird JR Jr, Suddath WO, Kent KM, Weissman NJ. Intravascular ultrasound assessment of the stenosis location and morphology in left main coronary artery in relation to anatomic left main length. *Am J Cardiol* 2001;88:1-4.

16. Park SJ, Hong MK, Lee CW, Kim JJ, Song JK, Kang DH, Park SW, Mintz GS. Elective stenting of unprotected left main coronary artery stenosis: effect of debulking before stenting and intravascular ultrasound guidance. *J Am Coll Cardiol* 2001;38:1054-60.

17. Black A Jr., Cortina R, Bossi I, Choussat R, Fajadet J, Marco J. Unprotected left main coronary artery stenting: correlates of midterm survival and impact of patient selection. *J Am Coll Cardiol* 2001;37:832-8.

18. Tan WA, Tamai H, Park SJ, Plokker HW, Nobuyoshi M, Suzuki T, Colombo A, Macaya C, Holmes DR Jr, Cohen DJ, Whitlow PL, Ellis SG; ULTIMA Investigators.Long-term clinical outcomes after unprotected left main trunk percutaneous revascularization in 279 patients. *Circulation* 2001;104:1609 -14.

19. Takagi T, Stankovic G, Finci L, Toutouzas K, Chieffo A, Spanos V, Liistro F, Briguori C, Corvaja N, Albero R, Sivieri G, Paloschi R, Di Mario C, Colombo A. Results and long-term predictors of adverse clinical events

after elective percutaneous interventions on unprotected left main coronary artery. *Circulation* 2002;106:698 -702.

20. Park SJ, Lee CW, Kim YH, Lee JH, Hong MK, Kim JJ, Park SW.Technical feasibility, safety, and clinical outcome of stenting of unprotected left main coronary artery bifurcation narrowing. *Am J Cardiol* 2002;90:374-8.

21. Park SJ, Park SW, Hong MK, Lee CW, Lee JH, Kim JJ, Jang YS, Shin EK, Yoshida Y, Tamura T, Kimura T, Nobuyoshi M. Long-term (three-year) outcomes after stenting of unprotected left main coronary artery stenosis in patients with normal left ventricular function. *Am J Cardiol* 2003;91:12-6.

22. Hu FB, Tamai H, Kosuga K, Kyo E, Hata T, Okada M, Nakamura T, Fujita S, Tsuji T, Takeda S, Motohara S, Uehata H. Intravascular ultrasound-guided directional coronary atherectomy for unprotected left main coronary stenoses with distal bifurcation involvement. *Am J Cardiol* 2003;92:936-40.

23. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med.* 2002;346:1773-1780.

24. Arampatzis CA, Lemos PA, Tanabe K, Hoye A, Degertekin M, Saia F, Lee CH, Ruiter A, McFadden E, Sianos G, Smits PC, van der Giessen WJ, de Feijter P, van Domburg R, Serruys PW. Effectiveness of sirolimus-eluting stent for treatment of left main coronary artery disease. *Am J Cardiol* 2003;92:327-9.

25. Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, Dudek D, Fort S, Schiele F, Zmudka K, Guagliumi G, Russell ME; TAXUS II Study Group. Randomized Study to Assess the Effectiveness of Slow and Moderate-Release Polymer-Based Paclitaxel-Eluting Stents for Coronary Artery Lesion. *Circulation.* 2003;108:788 -794.

26. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE; SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med.* 2003;349:1315-1323.

27. Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, Breithardt G; E-SIRIUS Investigators. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet.* 2003;362:1093-1099.

28. Arampatzis CA, Lemos PA, Hoye A, Saia F, Tanabe K, van der Giessen WJ, Smits PC, McFadden E, de Feyter P, Serruys PW. Elective sirolimus-eluting stent implantation for left main coronary artery disease: six-month angiographic follow-up and 1-year clinical outcome. *Cathet Cardiovasc Interv* 2004;62:292- 6.

29. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med.* 2004;350:221-231.

30. Park SJ, Kim YH, Lee BK, Lee SW, Lee CW, Hong MK, Kim JJ, Mintz GS, Park SW. Sirolimus-Eluting Stent Implantation for Unprotected Left Main Coronary Artery Stenosis. Comparison With Bare Metal Stent Implantation. *J Am Coll Cardiol* 2005, 45:351-356.

31. Chieffo A, Stankovic G, Bonizzoni E, Tsagalou E, Iakovou I, Montorfano M, Airoldi F, Michev I, Sangiorgi MG, Carlino M, Vitrella G, Colombo A.Early and Mid-Term Results of Drug-Eluting Stent Implantation in Unprotected Left Main. *Circulation* 2005; 111:791-795.

32. Colombo A, Stankovic G, Orlic D, Corvaja N, Liistro F, Airoldi F, Chieffo A, Spanos V, Montorfano M, Di Mario C. Modified T-stenting technique with crushing for bifurcation lesions: immediate results and 30-day outcome. *Cathet Cardiovasc Interv* 2003;60:145-51.

33. Colombo A, Moses JW, Morice MC, Ludwig J, Holmes DR Jr, Spanos V, Louvard Y, Desmedt B, Di Mario C, Leon MB. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation* 2004;109:1244 -9.

34. Tanabe K, Hoye A, Lemos PA, Aoki J, Arampatzis CA, Saia F, Lee CH, Degertekin M, Hofma SH, Sianos G, McFadden E, Smits PC, van der Giessen WJ, de Feyter P, van Domburg RT, Serruys PW.Restenosis rates following bifurcation stenting with sirolimus-eluting stents for de novo narrowings. *Am J Cardiol* 2004;94:115- 8.

CHAPTER 8

LATE AND VERY LATE STENT THROMBOSIS FOLLOWING DRUG-ELUTING STENT IMPLANTATION IN UNPROTECTED LEFT MAIN CORONARY ARTERY: A MULTICENTRE REGISTRY

Late and very late stent thrombosis following drug-eluting stent implantation in unprotected left main coronary artery: a multicentre registry

Alaide Chieffo[1], Seung-Jung Park[2], Emanuele Meliga[3], Imad Sheiban[4], Michael S. Lee[5], Azeem Latib[1], Young-Hak Kim[2], Marco Valgimigli[3], Dario Sillano[4], Valeria Magni[1], Giuseppe Biondi-Zoccai[4], Matteo Montorfano[1], Flavio Airoldi[1,6], Renata Rogacka[1], Mauro Carlino[1], Iassen Michev[1,6], Cheol-Whan Lee[2], Myeong-Ki Hong[2], Seong-Wook Park[2], Claudio Moretti[4], Erminio Bonizzoni[7], Giuseppe M. Sangiorgi[1,6], Jonathan Tobis[5], Patrick W. Serruys[3], and Antonio Colombo[1,6]*

[1]San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy; [2]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [3]Erasmus Medical Center, Thoraxcenter, Rotterdam, The Netherlands; [4]San Giovanni Battista Hospital Turin, Italy; [5]University of California, Los Angeles Medical Center, CA, USA; [6]EMO Centro Cuore Columbus, Milan, Italy; and [7]Institute of Medical Statistics and Biometry, University of Milan, Milan, Italy

Received 31 January 2008; revised 17 April 2008; accepted 29 May 2008; online publish-ahead-of-print 18 June 2008

See page 2064 for the editorial comment on this article (doi:10.1093/eurheartj/ehn342)

Aims To evaluate the occurrence of late and very late stent thrombosis (ST) following elective drug-eluting stent (DES) implantation in unprotected left main coronary artery (LMCA) stenosis in a large multicentre registry.

Methods and results All 731 consecutive patients who had sirolimus- or paclitaxel-eluting stent electively implanted in *de novo* lesions on unprotected LMCA in five centres were included. ST was defined according to Academic Research Consortium definitions. Four (0.5%) patients had a definite ST: three early (two acute and one subacute) and one late ST, no cases of very late definite ST were recorded. All patients survived from the event. Three patients had a probable ST. Therefore, 7/731 (0.95%) patients had a definite or a probable ST and all were on dual antiplatelet therapy at the time of the event. Possible (eight late and 12 very late) ST occurred in 20 (2.7%) patients. At 29.5 ± 13.7 months follow-up, a total of 45 (6.2%) patients had died; 31 (4.2%) of cardiac death. Ninety five (12.9%) patients had a target-vessel and 76 (10.4%) a target-lesion revascularization. Angiographic follow-up was performed in 548 patients (75%): restenosis occurred in 77 (14.1%) patients.

Conclusion Elective treatment of LMCA stenosis with DES appears safe with a 0.9% incidence of definite and probable ST at 29.5 ± 13.7 months.

Keywords Stent • Left main coronary artery • Drug-eluting stents • Stent thrombosis

Introduction

Some concerns have recently been raised regarding the risk of late and very late stent thrombosis (ST) following drug-eluting stent (DES) implantation.[1–10] Registry data of percutaneous coronary interventions (PCI) with DES use in unprotected left main coronary artery (LMCA) lesions showed that, at mid-term clinical follow-up, this is a feasible and safe approach.[11–19] To date, no study has specifically addressed the prevalence and predictors of late and very late ST following elective DES implantation in unprotected LMCA lesions. The aim of the present study is therefore to evaluate the occurrence of late and very late ST following elective DES implantation in unprotected LMCA stenosis in a large multicentre registry.

* Corresponding author: Tel: +39 02 2643 7331, Fax: +39 02 2643 7339, Email: colombo.antonio@hsr.it

Methods

This study included all consecutive patients with a stenosis in an unprotected LMCA electively treated with PCI and sirolimus- (SES, Cypher, Cordis, Johnson & Johnson Company, Warren, NJ, USA) or paclitaxel-eluting stent (PES, Taxus, Boston Scientific, Natick, MA, USA) implantation in five centres (San Raffaele Hospital and EMO Centro Cuore Columbus in Milan; San Giovanni Battista Hospital in Turin, Italy; Erasmus Medical Center – Thoraxcenter, The Netherlands; the Asan Medical Center, Korea and University of California, Los Angeles Medical Center) between March 2002 and March 2006. The data were prospectively collected in the single centres and retrospectively entered into a common database. Patients with ST or non-ST elevation myocardial infarctions (MIs) were excluded from the analysis. The decision to perform PCI instead of surgery was considered when one of these two conditions was present: suitable anatomy for stenting and preference by patient for a percutaneous approach or suitable anatomy for stenting and disincentive for surgery defined as a Euroscore ≥ 6 and/or prior coronary artery bypass grafting (CABG) with failure of all conduits.

Coronary angioplasty and DES implantation were performed according to the practice of fully covering the diseased segment.[20,21] At the start of the procedure, a bolus of unfractionated heparin was administered at 100 IU/kg to achieve an activated clotting time of >250 s. Glycoprotein IIb/IIIa inhibitors were administered at the discretion of the operator. Clinical follow-up was scheduled and obtained for all patients at 1, 6, 12, and 24 months by office visit or direct telephone call to the patients. Patients eligible for longer clinical follow-up were contacted at 36, 48, and 60 months.

Dual antiplatelet therapy (DAT) (i.e. aspirin 100 mg daily and clopidogrel 75 mg daily or ticlopidine 250 mg twice daily) was administrated according to local practice (for at least 6 months after the procedure in Rotterdam and Turin and 12 months in Milan, Seoul, and Los Angeles). All patients were advised to remain on aspirin (100 mg die) lifelong. In addition, cilostazol was also given to some patients for 1 month (in Seoul).

Detailed information on adherence as well as reasons and date for discontinuation of DAT was obtained in all patients.

Angiographic follow-up was scheduled between 4 and 9 months or earlier if non-invasive evaluation or clinical presentation suggested the presence of ischaemia.

Definitions

ST was defined on the basis of the Academic Research Consortium definitions according to the timing of presentation as early (0–30 days), late (31–360 days), or very late (>360 days) and to the following trilevel of certainty:

Definite ST in the presence of an acute coronary syndrome and either angiographic or pathological (autopsy) confirmation of ST;

Probable ST in case of an acute MI involving the target-vessel territory without angiographic confirmation of thrombosis or other identified culprit lesion and/or any unexplained death within 30 days;

Possible ST in the case of any unexplained death after 30 days.

The following major adverse cardiac events (MACE), during hospital stay and at follow-up, were also analysed: death, CABG, MI, target lesion revascularization (TLR), and target vessel revascularization (TVR).

Deaths were classified as either cardiac or non-cardiac. Cardiac death was defined as any death due to a cardiac cause (e.g. MI, low-output failure, fatal arrhythmia), procedure-related deaths, and death of unknown cause.

Non-Q-wave MI was defined as an elevation of serum creatine kinase (CK) MB isoenzyme that was three times the upper limit of normal (ULN) in the absence of pathological Q-waves.

Restenosis was defined as >50% luminal narrowing at the segment site (stent and 5 mm proximal and distal) demonstrated at the follow-up angiography, regardless of clinical symptoms.

TLR was defined as any revascularization performed on the treated segment; TVR was defined as any re-intervention performed on the treated vessel considering also treatment of any segment in the left anterior descending and circumflex arteries.

The European system for cardiac operative risk evaluation (Euroscore) was used to stratify the risk of death at 30 days.[22] The patients were stratified as high risk in the presence of a Euroscore ≥ 6.

Unstable angina was defined according to the presence of: (i) rest angina (usually >20 min); (ii) new onset (<2 months) severe exertion angina of at least Canadian Cardiovascular Society Classification (CCSC) class III in severity; (iii) recent (<2 months) acceleration of angina as reflected by an increase of at least one CCSC class to at least CCSC class III.

Event adjudication

All the events in patients included in this registry were first evaluated by at least two co-authors from the participating centres and then by two co-authors of the coordinating centre on the basis of detailed reports from each of the participating centres.

Statistical analysis

Continuous data were reported as mean $\pm$ standard deviation (SD) or median [interquartile range (IQR)] as appropriate. In general, differences in proportions were tested with χ^2 test or Fisher's exact test, while differences in continuous variables with Student's *t*-test or Wilcoxon rank sum test.

At univariate logistic regression analysis the following covariates were assessed: age, gender, diabetes, left ventricular ejection fraction (LVEF), unstable angina, Euroscore, DAT, duration of DAT (<6 months, 6–12 months, >12 months), distal LMCA, intravascular ultrasound (IVUS) guidance, baseline reference vessel diameter, baseline minimal luminal diameter, stent type, both branch stenting, crush technique, stent length, final kissing balloon inflation, and maximum inflation pressures. Among continuous variable, no pre-specified cut-off was employed. Because of the small number of events observed in a dataset of 731 patients, exact odds ratios (OR) with associated 95% confidence intervals (CI) and two-tailed *P*-values were computed using permutation resampling.

In order to obtain parameter estimates adjusted for potential collinearity among covariates, exact conditional analyses were carried out re-running the exact logistic regressions with one covariate at a time as a fixed factor and treating the remaining as nuisance parameters.[23] The Statistical Analysis System program version 9.1 (SAS Institute, Cary, NC, USA) was used for data analysis.

All authors have read and agreed to the manuscript as written.

Results

Baseline clinical, lesion, and procedural characteristics are summarized, respectively, in *Tables 1* and 2. A total of 731 patients with unprotected LMCA were electively treated in our centres with DES implantation. One hundred and seventy six (24.0%) patients were diabetic and 333 (45.5%) had unstable angina. Mean age was 63.1 $\pm$ 11.8 years and LVEF 54.8 $\pm$ 10.9%. Median and IQR of Euroscore was 3.0 (2.0–6.0); a Euroscore ≥ 6 was present in

Table 1 Clinical characteristics of the study population

	$n = 731$ patients
Age (years)	63.1 ± 11.8
Female gender, *n* (%)	189 (25.8)
Hypertension, *n* (%)	427 (58.4)
Hypercholesterolaemia, *n* (%)	368 (50.3)
Smoking, *n* (%)	247 (33.8)
Diabetes mellitus, *n* (%)	176 (24.0)
Unstable angina, *n* (%)	333 (45.5)
LVEF (%)	54.8 ± 10.9
Chronic renal failure, *n* (%)	40 (5.5)
Euroscore, median (IQR)	3.0 (2.0–6.0)
Euroscore ≥6, *n* (%)	262 (35.8)

LVEF, left ventricular ejection fraction (%).
Continuous data were reported as mean ± SD or median and interquartile range (IQR) as appropriate.

Table 2 Lesion and procedural characteristics

	$n = 731$ patients
Distal, *n* (%)	559 (76.5)
Number of vessels treated	2.2 ± 0.8
Number of lesions treated	2.3 ± 1.5
IABP, *n* (%)	96 (13.1)
GP IIb/IIIa inhibitors usage, *n* (%)	102 (13.9)
IVUS guidance, *n* (%)	337 (46.1)
DCA or rotablator, *n* (%)	24 (3.3)
Cypher stent implantation, *n* (%)	536 (73.3)
Taxus stent implantation, *n* (%)	196 (26.8)
Both branches stented/distal, *n* (%)	276 (49.4)
Stent length (mm)	25.0 ± 15.1
Maximum balloon diameter (mm)	3.7 ± 0.6
Maximum pressure inflation (atm)	17.5 ± 3.7

IABP, intra-aortic balloon pump implantation; GP IIb/IIIa inhibitors usage, use of glycoprotein IIb/IIIa inhibitors during the procedure; IVUS, intravascular ultrasound; DCA, directional coronary atherectomy.
Data are presented as percentages and mean ± SD.

36% of the patients. The number of treated vessels was 2.2 ± 0.8 and the number of lesions 2.3 ± 1.5; 27% of the patients also had right coronary artery disease. An intra-aortic balloon pump was used in 96 (13.1%) patients. In 337 (46.1%) patients IVUS guidance was performed. Reference vessel diameter of the LMCA was 3.7 ± 0.6 mm. At least one SES was implanted in 536 (73.3%) and PES in 196 (26.8%) patients; in one patient both PES and SES were used. In 559 (76.5%) patients the stenosis was located at the distal segment of the LMCA. When the distal left main was treated, the stenting strategy adopted was provisional (cross-over) approach in 283 (50.6%) patients, 'crush' in 120 (21.5%), 'V' stenting in 80 (14.3%), 'modified T' in 52 (9.3%) and 'culotte' in 24 (4.3%). Final kissing balloon inflation was performed in 64% of the cases.

The median duration of DAT was 8.8 months (IQR, 6.0–20.7).

Stent thrombosis

Definite stent thrombosis

Four (0.54%) patients had a definite ST. Three patients had an early (two acute and one subacute) and only one a late definite ST.

Early definite stent thrombosis

Among the three patients with early definite ST: one had an intra-procedural ST successfully treated with intravenous administration of abciximab, intracoronary administration of recombinant tissue plasminogen activator (r-TPA) and additional stent implantation (the patient was found to be a poor responder to clopidogrel); the second occurred some hours after the PCI and was successfully treated with emergency CABG; and the last occurred 12 days after the index procedure. All the three patients had the thrombotic event while on DAT and all of them are alive at the time of this report.

Late and very late definite stent thrombosis

Only one patient had a definite late ST at 3.9 months while on DAT. The patient had an acute anterior MI and angiographically proven ST in the proximal left anterior descending artery successfully treated with repeat PCI. This patient died of lung cancer 10 months after the thrombotic event. No cases of very late definite ST were recorded.

Probable stent thrombosis

Probable ST occurred in three patients. In all the three, the event occurred early and was adjudicated because of the occurrence of sudden death within 30 days from the procedure, in the absence of an autopsy or control angiography.

Therefore, a total of 7/731 (0.95%) patients had a definite or probable ST. Characteristics of patients with definite or probable ST are illustrated in *Table 3*; baseline, lesion, procedural characteristics of patients with definite or probable ST vs. patients without definite or probable ST are illustrated in *Table 4*.

At univariate exact logistic (unconditional) analysis, age (OR = 1.07, CI 95% 1.00–1.16; $P = 0.03$), LVEF (OR = 0.94, CI 95% 0.90–0.98; $P = 0.007$) and Euroscore (OR = 1.19, CI 95% 1.07–1.34; $P = 0.003$) were correlated to definite or probable ST. At conditional univariate analysis, only LVEF (OR = 0.94, CI 95% 0.89–0.99; $P = 0.03$) and Euroscore (OR = 1.22, CI 95% 1.06–1.41; $P = 0.008$) were associated with definite or probable ST (*Table 5* and *Figure 1A*).

Possible stent thrombosis

Possible stent thrombosis was adjudicated in 20 patients in whom the cause of death was unexplained (no autopsy or control angiography was performed).

Late possible ST occurred in eight and very late possible ST in 12 of these patients. Eight of these patients were on DAT at the time of the event and 12 had suspended DAT (10 because of the hospital protocol, one because of gastric symptoms and

Table 3 Characteristics of the patients with definite and probable stent thrombosis

Patient	Euro score	Age (years)	LVEF (%)	Unstable angina	Lesion location	Stent type	Stenting technique	Time of the event (days)	DAT at the time of the event
Definite ST									
1	1	55	55	No	Distal	Taxus	Crush	0	Yes
2	9	72	30	Yes	Distal	Cypher	Cross-over	0	Yes
3	10	71	45	Yes	Distal	Taxus	V	12	Yes
4	11	71	35	No	Distal	Taxus	Crush	116	Yes
Probable ST									
1	12	76	40	Yes	Distal	Cypher	Crush	12	Yes
2	15	78	39	Yes	Ostium	Taxus	Cross-over	1	Yes
3	10	85	30	Yes	Distal	Cypher	Cross-over	3	Yes

LVEF, left ventricular ejection fraction; DAT, dual antiplatelet therapy; ST, stent thrombosis.

Table 4 Baseline, lesion, procedural characteristics of patients with definite or probable stent thrombosis vs. patients without definite or probable stent thrombosis

	Patients with definite or probable stent thrombosis ($n = 7$)	Patients without definite or probable stent thrombosis ($n = 724$)
Age (years)	72.5 ± 9.2	63.1 ± 11.8
LVEF (%)	39.1 ± 8.8	54.9 ± 10.8
Male gender	5 (71.5%)	537 (74.1%)
Unstable angina	5 (71.5%)	328 (45.3%)
Diabetes	2 (28.5%)	174 (24.1%)
Euroscore	9.6 ± 4.6	4.0 ± 3.0
Distal location	6 (85.7%)	554 (76.5%)
Both branch stenting[a]	4 (66.6%)	272 (49.1%)
Stent length (mm)	25.8 ± 14.0	25.0 ± 15.8
Reference vessel (mm)	3.32 ± 1.0	3.4 ± 0.5
IVUS done	3 (42.1%)	334 (46.8%)
DAT	7 (100%)	117 (16.1%)
Myocardial infarction[b]	4 (57.1%)	9 (1.24%)
Target lesion revascularization	4 (57.1%)	74 (10.2%)
Cardiac death	3 (42.8%)	28 (3.86%)

DAT, dual antiplatelet therapy at the time of the thrombotic event [in patients with definite or probable stent thrombosis (ST)] or at the time of last clinical follow-up (in patients without definite or probable ST).
[a]Both branch stenting: the percentages are calculated considering only patients with distal lesion location.
[b]In myocardial infarctions are excluded peri-procedural myocardial infarctions unless occurred following ST.

one because of abdominal surgery). Clinical characteristics were unfavourable in most of these patients: 8/20 (40%) were >75 years old, 13/20 (65%) patient had a LVEF <40% and a Euroscore ≥6 (*Table 6*).

In-hospital and long-term major adverse cardiac events

In-hospital and long-term clinical outcomes are illustrated in *Table 7*.

During hospitalization, five (0.68%) patients died; all of them were >75 years and had a Euroscore >6. None of these patients had an angiographically or pathologically proven ST. Sudden death occurred in 2/5, and probable ST cannot be excluded. Non-Q-wave MI occurred in 69 (9.4%) of the patients.

At 29.5 ± 13.7 months, cumulatively 45 (6.2%) patients died; 31 (4.2%) of cardiac death. During the follow-up period, 11 patients experienced a MI and nine of them were not in the target vessel (two were due to angiographically proven ST in a stent not in the target vessel). Seventy six (10.5%) patients underwent TLR and 95 (13.0%) a TVR (83 re-PCIs and 12 CABG). Angiographic follow-up was performed in 548 patients (75%); restenosis occurred in 77 (14.1%) of these patients. Notably, the range and extent of clinical follow-up did not differ among the different centres.

At univariate exact logistic (unconditional) analysis, age (OR = 1.06, CI 95% 1.03–1.09; $P = 0.0001$), LVEF (OR = 0.94, CI 95% 0.92–0.96; $P < 0.0001$), Euroscore (OR = 1.21, CI 95% 1.13–1.30; $P < 0.0001$), unstable angina (OR = 3.73, CI 95% 1.54–11.6; $P = 0.002$) and IVUS guidance (OR = 0.93, CI 95% 0.16-0.93; $P = 0.03$) were correlated to cardiac death. At conditional analysis, only unstable angina (OR = 3.25, CI 95% 1.33–9.05; $P = 0.007$), LVEF (OR = 0.79, CI 95% 0.87–0.97; $P = < 0.0001$) and Euroscore (OR = 1.18, CI 95% 1.04–1.23; $P = 0.003$) were correlated to cardiac death (*Figure 1B*).

Discussion

The main findings of this study are: (i) the incidence of definite ST is relatively low (0.5%): 75% of the cases occurred within 30 days and none after 1 year; all the patients were successfully treated and survived from the event; (ii) the cumulative occurrence of definite and probable ST is 0.95% and at conditional analysis exact logistic analysis was correlated with the Euroscore and LVEF, but not with

Table 5 Unconditional and conditional analysis of the predictors of definite and probable stent thrombosis

	Unconditional analysis			Conditional analysis		
	OR	95% exact CI	P	OR	95% exact CI	P
DES type	0.5174	0.1950–1.2693	0.1728	0.5531	0.2081–1.3732	0.2420
Gender	0.8708	0.1409–9.2236	1.0000	0.6773	0.1044–7.4699	0.9417
Age (years)	1.0783	1.0052–1.1620	0.0343	1.0649	0.9860–1.1595	0.1154
Diabetes	1.2503	0.1182–7.7574	1.0000	0.8982	0.0814–5.8378	1.0000
Unstable angina	3.0184	0.4903–31.9183	0.3171	2.7247	0.4283–29.6316	0.4045
LVEF (%)	0.9436	0.9027–0.9829	0.0072	0.9417	0.8894–0.9934	0.0280
Reference vessel (mm)	1.1958	0.5949–2.9384	0.7899	1.2420	0.5879–3.4065	0.7482
MLD (mm)	0.9489	0.2923–3.0104	0.9327	1.2245	0.3775–3.9770	0.7357
Maximum pressure (atm)	1.1592	0.9807–1.3545	0.0798	1.1639	0.9775–1.3656	0.0862
Stent length (mm)	1.0055	0.9552–1.0474	0.7544	1.0152	0.9573–1.0656	0.5395
Distal location	1.8425	0.2208–85.4474	0.9695	0.7260	0.0460–55.1541	1.0000
Kissing balloon inflation	1.9497	0–4.9615	1.0000	2.2424	0–6.0158	1.0000
Type of stenting technique	1.9465	0.3910–9.6902	0.6171	1.5316	0.2979–7.8749	1.0000
Both branch stenting	3.1327	0.4454–34.8600	0.3339	2.2919	0.3134–26.3552	0.5863
Euroscore	1.1996	1.0758–1.3422	0.0026	1.2193	1.0577–1.4124	0.0076
IVUS	0.8758	0.1273–5.2108	1.0000	1.4492	0.2006–9.1331	0.9194
DAT discontinuation	0.1464	0.0219–0.8813	0.0347	0.1524	0.0196–0.9889	0.0485
DAT duration, 12 months	0.6076	0.1193–2.2452	0.8555	0.4343	0.0836–1.6713	0.3823
DAT duration, 6 months	1.2958	0.2753–4.4804	1.0000	1.3891	0.2899–4.9297	1.0000

DES, drug-eluting stent; MLD, minimal lumen diameter; IVUS, intravascular ultrasound; DAT, dual antiplatelet therapy.

the duration of DAT (at the time of the thrombotic event all patients were on DAT); (iii) there was a 4.2% cumulative cardiac mortality and 6.2% cumulative total mortality rate at 29.5 ± 13.7 months follow-up.

According to current European Society of Cardiology and American Heart Association/American College of Cardiology guidelines the presence of a stenosis in the LMCA (if a patient is not eligible for CABG) is considered a Class IIb or IIa indication for PCI, respectively.[24,25] According to these guidelines, when a patient is eligible for CABG, PCI has a class III indication, irrespective of the lesion location. Some retrospective studies evaluating surgical treatment for this disease reported an in-hospital mortality varying from 1.7 to 7.0% and a 1-year mortality of 6–14%.[26–30] Recently, encouraging results have been reported with elective DES implantation in LMCA with a 1-year mortality of 0–5%.[11,13,17,31] The need for TLR in these registries varied from 0 to 14%.[11,13,17,19,31] Indeed, the presence of ostial and mid-shaft lesions in the LMCA was associated with a more favourable outcome and an extremely low restenosis rate.[12,32]

Recently some concerns have been raised about the long-term safety of DES implantation.[1–10] A multicentre registry analysing >3000 patients electively treated with DES (in 67% for an off-label indication) reported a ST incidence, at 18 months, of 1.9% (which included definite and possible ST).[1] Half of the events occurred within 30 days. Similarly, another registry reported that most (60%) ST occurs within 30 days.[3] In this study, which included patients with acute coronary syndromes, a 2.9% cumulative incidence of definite ST was reported in 8146 patients at 3 years. The presence of an acute coronary syndrome was an independent predictor of ST.

No study has thus far addressed the issue of ST following DES implantation in the subset of unprotected LMCA lesions. Our study represents the largest ($n = 731$) series of patients with unprotected LMCA lesions electively treated with DES. According to clinical and lesion characteristics, our study population was at moderately low surgical risk (Euroscore ≥ 6 in almost 36% of the patients), but at intermediate risk for angioplasty (distal left main in 76% of the patients). The occurrence of in-hospital MACE, which included non-Q-wave MI (defined as an elevation of serum CK MB isoenzyme that was three times ULN), was in accordance with previous reports. Only four (0.5%) patients had a definite ST and all of them were on DAT at the time of the event. This finding may point out the importance of evaluating individual responsiveness to antiplatelet therapy.[33] Interestingly one patient, who developed intra-procedural ST and in whom we measured platelet inhibition, was found to be a non-responder to clopidogrel. In three (75%) patients, definite ST occurred within 30 days and only in one at 3.9 months. All the four patients who had definite ST survived from the event after having been successfully treated: three with repeat PCI and one with CABG. Three of the patients are still alive at the time of this report and one died because of lung cancer.

Even if we consider definite and probable ST together (which included three deaths within 30 days in the absence of angiographic or pathological confirmation of ST) the low incidence of 0.95% is still quite reassuring. Again, all patients had the event while on

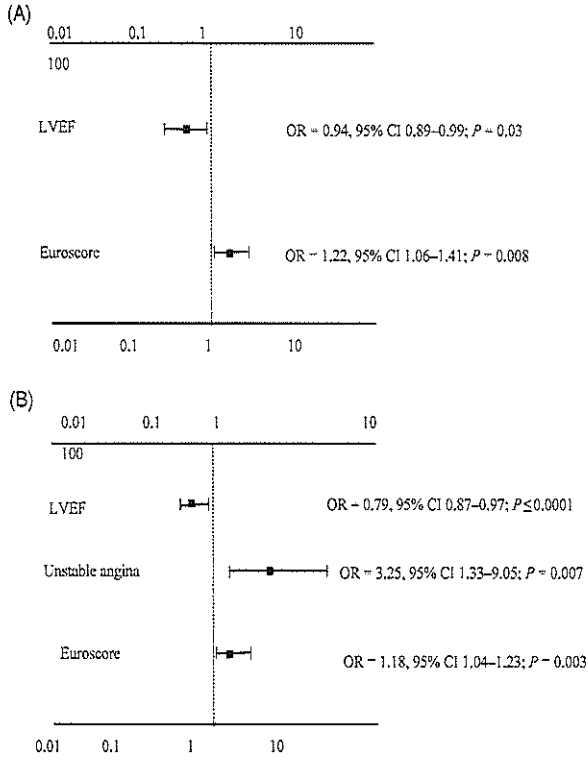


Figure 1 Predictors at conditional analysis of definite or probable stent thrombosis (*A*) and cardiac death (*B*).

DAT. At conditional exact logistic analysis, the occurrence of definite and probable ST was correlated with Euroscore and LVEF. This finding is consistent with predictors identified in general PCI populations.[1,3] Therefore, no unique ST predictor among LMCA lesions was identified in our analysis.

Regarding the 20 (2.7%) patients with possible ST (unexplained deaths after 30 days) we need to take into account that many of these patients had high risk characteristics for cardiac death unrelated to ST (*Table 6*); at conditional exact logistic analysis, cardiac death was correlated to Euroscore and LVEF. Moreover, at least nine of the patients with probable ST would meet the inclusion criteria for MADIT II (multicentre automatic defibrillator implantation trial), which reported an expected overall mortality of 19.8% and a sudden cardiac death rate of 9.8% at 2 years in the control group.[34,35] Eight patients were still on DAT at the time of death and 12 were not (10 suspended DAT according to the hospital protocol and only two prematurely).

Furthermore, the cumulative occurrence of death (cardiac and non-cardiac) at 29.5 ± 13.7 months follow-up was 4.2 and 6.2%, respectively. These rates are encouraging if compared with mortality rates following CABG at a similar clinical follow-up time period.

The low rates of cardiac death in our study could also be justified by the exclusion of patients presenting with a MI. In addition, we cannot exclude that the low rate of cardiac events reported in our study were due to the fact that LM stenting was performed in highly experienced centres.

Additionally, only 11 (1.5%) patients experienced a MI during follow-up, nine of which were not in the target vessel. Interestingly, two were due to angiographically proven ST not in the target vessel.

In our registry the long-term efficacy of DES in this subset of lesions is confirmed by a TLR and TVR rate (83 re-PCIs and 12 CABG) of 10 and 13%, respectively, and a restenosis rate of 14% even with 76% of lesions involving the distal LMCA. So far, no randomized data comparing PCI with DES implantation vs. CABG are available.[11,15,16] The 'Synergy between Percutaneous Intervention with TAXUS® and Cardiac Surgery' (SYNTAX) trial was recently conducted and included 710 patients with left main disease randomized to receive either a PES or CABG. Interestingly, the study was not powered to detect any difference between CABG and PCI with DES in the subset of unprotected LMCA lesions but only in triple-vessel disease.

Table 6 Characteristics of the patients with possible stent thrombosis

Patient	Euro score	Age (years)	LVEF (%)	Unstable angina	Lesion location	Stent type	Stenting technique	Time of the event (days)	DAT at the time of the event
1	8	72	26	No	Distal	Cypher	Cross-over	1162	No
2	5	65	55	No	Distal	Cypher	V	175	No
3	0	48	57	Yes	Distal	Cypher	Cross-over	790	No
4	3	53	61	Yes	Distal	Cypher	Crush	546	No
5	13	82	28	Yes	Distal	Cypher	Crush	154	No
6	7	66	35	Yes	Distal	Cypher	Cross-over	1390	Yes
7	11	71	20	Yes	Distal	Taxus	Crush	443	Yes
8	4	63	65	No	Distal	Taxus	Crush	955	No
9	5	54	35	No	Distal	Cypher	V	986	Yes
10	4	72	30	No	Distal	Cypher	Cross-over	623	Yes
11	9	77	30	Yes	Distal	Taxus	Cross-over	270	No
12	11	80	30	Yes	Distal	Taxus	Culotte	156	No
13	6	56	40	Yes	Distal	Taxus	Cross	699	No
14	8	75	45	Yes	Ostium	Cypher	N/A	1149	No
15	10	72	40	Yes	Distal	Taxus	Culotte	352	No
16	9	80	30	Yes	Distal	Taxus	Cross-over	243	No
17	4	78	60	Yes	Distal	Taxus	Cross-over	482	Yes
18	11	82	30	No	Distal	Taxus	Cross-over	180	Yes
19	10	51	25	Yes	Distal	Cypher	Cross-over	757	Yes
20	25	81	50	Yes	Ostium	Taxus	N/A	99	Yes

LVEF, left ventricular ejection fraction; DAT, dual antiplatelet therapy; N/A, not applicable.

Table 7 Major adverse cardiac event at hospitalization and at long-term clinical follow-up

	In-hospital, $n = 731$	Follow-up, $n = 726$
Cardiac death, *n* (%)	5 (0.7)	26 (3.6)
Total death, *n* (%)	5 (0.7)	40 (5.5)
MI, *n* (%)	69 (9.4)	11 (1.5%)
TLR, *n* (%)	2 (0.3)	76 (10.5)
TVR, *n* (%)	2 (0.3)	95 (13.0)
MACE, *n* (%)	73 (9.9%)	138 (19.0)

MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; MACE, major adverse cardiac events.
Data are presented as percentages.

Study limitations

This is a retrospective multicentre registry. No '*a priori*' sample size has been calculated. Another limitation is the length of clinical follow-up. Moreover we cannot exclude that some of the unexplained deaths that occurred at follow-up could have been a ST because of the absence of an angiographic and/or pathological examination. Different durations of DAT were prescribed among the centres due to different institutional practices.

Conclusions

In this multicentre registry, the elective use of DES in unprotected LMCA stenosis appears to be safe and effective at 29.5 ± 13.7 clinical follow-up. Definite and probable ST occurred in 0.9% of the patients. Further studies with longer durations of follow-up as well as uniform and prespecified durations of DAT are needed in order to better clarify the issue of safety following DES implantation in unprotected LMCA lesions.

Conflict of interest: the authors do not have any financial associations to disclose that might pose a conflict of interest in connection with the submitted article.

References

1. Airoldi F, Colombo A, Morici N, Latib A, Cosgrave J, Buellesfeld L, Bonizzoni E, Carlino M, Gerckens U, Godino C, Meizi G, Michev I, Montorfano M, Sangiorgi GM, Qasim A, Chieffo A, Briguori C, Grube E. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. *Circulation* 2007;**116**:745–754.
2. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007; **356**:989–997.
3. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Juni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* 2007;**369**:667–678.

4. Farb A, Boam AB. Stent thrombosis redux – the FDA perspective. *N Engl J Med* 2007;**356**:984–987.
5. Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H, Menichelli M, Sabate M, Suttorp MJ, Baumgart D, Seyfarth M, Pfisterer ME, Schomig A. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007;**356**:1030–1039.
6. Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin L. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med* 2007;**356**:1009–1019.
7. Maisel WH. Unanswered questions – drug-eluting stents and the risk of late thrombosis. *N Engl J Med* 2007;**356**:981–984.
8. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007;**356**:1020–1029.
9. Shuchman M. Debating the risks of drug-eluting stents. *N Engl J Med* 2007;**356**:325–328.
10. Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007;**356**:998–1008.
11. Chieffo A, Morici N, Maisano F, Bonizzoni E, Cosgrave J, Montorfano M, Airoldi F, Carlino M, Michev I, Melzi G, Sangiorgi G, Alfieri O, Colombo A. Percutaneous treatment with drug-eluting stent implantation versus bypass surgery for unprotected left main stenosis: a single-center experience. *Circulation* 2006;**113**:2542–2547.
12. Chieffo A, Park SJ, Valgimigli M, Kim YH, Daemen J, Shelban I, Truffa A, Montorfano M, Airoldi F, Sangiorgi G, Carlino M, Michev I, Lee CW, Hong MK, Park SW, Moretti C, Bonizzoni E, Rogacka R, Serruys PW, Colombo A. Favorable long-term outcome after drug-eluting stent implantation in nonbifurcation lesions that involve unprotected left main coronary artery: a multicenter registry. *Circulation* 2007;**116**:158–162.
13. Chieffo A, Stankovic G, Bonizzoni E, Tsagalou E, Iakovou I, Montorfano M, Airoldi F, Michev I, Sangiorgi MG, Carlino M, Vitrella G, Colombo A. Early and mid-term results of drug-eluting stent implantation in unprotected left main. *Circulation* 2005;**111**:791–795.
14. de Lezo JS, Medina A, Pan M, Delgado A, Segura J, Pavlovic D, Melian F, Romero M, Burgos L, Hernandez E, Urena I, Herrador J, Rapamycin-eluting stents for the treatment of unprotected left main coronary disease. *Am Heart J* 2004;**148**:481–485.
15. Lee MS, Kapoor N, Jamal F, Czer L, Aragon J, Forrester J, Kar S, Dohad S, Kass R, Eigler N, Trento A, Shah PK, Makkar RR. Comparison of coronary artery bypass surgery with percutaneous coronary intervention with drug-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol* 2006;**47**:864–870.
16. Palmerini T, Marzocchi A, Marrozzini C, Ortolani P, Sala F, Savini C, Bacchi-Reggiani L, Gianstefani S, Varzi S, Manara F, Kiros Weldeab M, Marinelli G, Di Bartolomeo R, Branzi A. Comparison between coronary angioplasty and coronary artery bypass surgery for the treatment of unprotected left main coronary artery stenosis (the Bologna Registry). *Am J Cardiol* 2006;**98**:54–59.
17. Park SJ, Kim YH, Lee BK, Lee SW, Lee CW, Hong MK, Kim JJ, Mintz GS, Park SW. Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis: comparison with bare metal stent implantation. *J Am Coll Cardiol* 2005;**45**:351–356.
18. Price MJ, Cristea E, Sawhney N, Kao JA, Moses JW, Leon MB, Costa RA, Lansky AJ, Teirstein PS. Serial angiographic follow-up of sirolimus-eluting stents for unprotected left main coronary artery revascularization. *J Am Coll Cardiol* 2006;**47**:871–877.
19. Valgimigli M, van Mieghem CAG, Ong ATL, Aoki J, Rodriguez Granillo GA, McFadden E, Kappetein AP, de Feijter P, Smits PC, Regar E, van der Giessen WJ, Slanos G, de Jaegere P, Van Domburg RT, Serruys PW. Short- and Long-term Clinical Outcome after Drug-Eluting Stent Implantation for the Percutaneous Treatment of Left Main Coronary Artery Disease. *Circulation* 2005;**111**:1383–1389.
20. Chieffo A, Bonizzoni E, Orlic D, Stankovic G, Rogacka R, Airoldi F, Mikhail GW, Montorfano M, Michev I, Carlino M, Colombo A. Intraprocedural stent thrombosis during implantation of sirolimus-eluting stents. *Circulation* 2004;**109**:2732–2736.
21. Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, Dudek D, Fort S, Schiele F, Zmudka K, Guagliumi G, Russell ME. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 2003;**108**:788–794.
22. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999;**16**:9–13.
23. Mehta CR, Patel NR. Exact logistic regression: theory and examples. *Stat Med* 1995;**14**:2143–2160.
24. Silber S, Albertsson P, Aviles FF, Camici PG, Colombo A, Hamm C, Jorgensen E, Marco J, Nordrehaug JE, Ruzyllo W, Urban P, Stone GW, Wijns W. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J* 2005;**26**:804–847.
25. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, Jacobs AK, Kern MJ, King SB, Morrison DA, O'Neill WW, Schaff HV, Whitlow PL, Williams DO, Antman EM, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention–summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 guidelines for percutaneous coronary intervention). *Circulation* 2006;**113**:156–175.
26. Beauford RB, Saunders CR, Lunceford TA, Niemeler LA, Shah S, Karanam R, Prendergast T, Burns P, Sardari F, Goldstein DJ. Multivessel off-pump revascularization in patients with significant left main coronary artery stenosis: early and midterm outcome analysis. *J Card Surg* 2005;**20**:112–118.
27. d'Allonnes FR, Corbineau H, Le Breton H, Leclercq C, Leguerrier A, Daubert C. Isolated left main coronary artery stenosis: long term follow up in 106 patients after surgery. *Heart* 2002;**87**:544–548.
28. Hannan EL, Wu C, Smith CR, Higgins RS, Carlson RE, Culliford AT, Gold JP, Jones RH. Off-pump versus on-pump coronary artery bypass graft surgery: differences in short-term outcomes and in long-term mortality and need for subsequent revascularization. *Circulation* 2007;**116**:1145–1152.
29. Holm F, Lubanda JC, Semrad M, Rohac J, Vondracek V, Miler I, Vanek I, Golan L, Aschermann M. [Main clinical and surgical determinants of in-hospital mortality after surgical revascularization of left main coronary artery stenosis: 2 year retrospective study (1998–1999)]. *J Mal Vasc* 2004;**29**:89–93.
30. Lu JC, Grayson AD, Pullan DM. On-pump versus off-pump surgical revascularization for left main stem stenosis: risk adjusted outcomes. *Ann Thorac Surg* 2005;**80**:136–142.
31. Sheiban I, Meliga E, Moretti c, Fumagalli A, Omedè P, Sciuto F, Grossomarra W, Trevi G. Sirolimus-eluting stents vs. bare metal stents for the treatment of unprotected left main coronary artery stenosis. *Eurointervention* 2006;**2**:356–362.
32. Colombo A, Chieffo A. Drug-eluting stent update 2007: part III: technique and unapproved/unsettled indications (left main, bifurcations, chronic total occlusions, small vessels and long lesions, saphenous vein grafts, acute myocardial infarctions, and multivessel disease). *Circulation* 2007;**116**:1424–1432.
33. Buonamici P, Marcucci R, Migliorini A, Gensini GF, Santini A, Paniccia R, Moschi G, Gori AM, Abbate R, Antoniucci D. Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. *J Am Coll Cardiol* 2007;**49**:2312–2317.
34. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**:877–883.
35. Greenberg H, Case RB, Moss AJ, Brown MW, Carroll ER, Andrews ML. Analysis of mortality events in the multicenter automatic defibrillator implantation trial (MADIT-II). *J Am Coll Cardiol* 2004;**43**:1459–1465.

The above article uses a new reference style being piloted by the EHJ that shall soon be used for all articles.

CHAPTER 9

A COLLABORATIVE SYSTEMATIC REVIEW AND META-ANALYSIS ON 1278 PATIENTS UNDERGOING PERCUTANEOUS DRUG-ELUTING STENTING FOR UNPROTECTED LEFT MAIN CORONARY ARTERY DISEASE

A collaborative systematic review and meta-analysis on 1278 patients undergoing percutaneous drug-eluting stenting for unprotected left main coronary artery disease

Giuseppe G.L. Biondi-Zoccai, MD,[a,o] Marzia Lotrionte, MD,[b,o] Claudio Moretti, MD,[a] Emanuele Meliga, MD,[a] Pierfrancesco Agostoni, MD,[c] Marco Valgimigli, MD, PhD,[d,e] Angela Migliorini, MD,[f] David Antoniucci, MD,[f] Didier Carrié, MD,[g] Giuseppe Sangiorgi, MD,[h,i] Alaide Chieffo, MD,[h,i] Antonio Colombo, MD,[h,i] Matthew J. Price, MD,[j] Paul S. Teirstein, MD,[j] Evald H. Christiansen, MD,[k] Antonio Abbate, MD,[l] Luca Testa, MD,[b] Julian P.G. Gunn, MD,[m] Francesco Burzotta, MD,[b] Antonio Laudito, MD,[n] Gian Paolo Trevi, MD,[a] and Imad Sheiban, MD[a] *Turin, Rome, Ferrara, Gussago, Florence, and Milan, Italy; Antwerp, Belgium; Toulouse, France; La Jolla, CA; Aarhus, Denmark; Richmond, VA; and Sheffield, United Kingdom*

Background Cardiac surgery is the standard treatment for unprotected left main disease (ULM). Drug-eluting stent (DES) implantation has been recently reported in patients with ULM but with unclear results. We systematically reviewed outcomes of percutaneous DES implantation in ULM.

Methods Several databases were searched for clinical studies reporting on ≥20 patients and ≥6-month follow-up. The primary end point was major adverse cardiovascular events (MACEs; ie, death, myocardial infarction, or target vessel revascularization [TVR]) at the longest follow-up. Incidence and adjusted risk estimates were pooled with generic inverse variance random-effect methods (95% CIs).

Results From 823 initial citations, 16 studies were included (1278 patients, median follow-up 10 months). Eight were uncontrolled registries, 5 nonrandomized comparisons between DES and bare-metal stents and 3 nonrandomized comparisons between DES and CABG, with no properly randomized trial. Meta-analysis for DES-based PCI showed, at the longest follow-up, rates of 16.5% (11.7%-21.3%) MACE, 5.5% (3.4%-7.7%) death, and 6.5% (3.7%-9.2%) TVR. Comparison of DES versus bare-metal stent disclosed adjusted odds ratios for MACE of 0.34 (0.16-0.71), and DES versus CABG showed adjusted odds ratios for MACE plus stroke of 0.46 (0.24-0.90). Meta-regression showed that disease location predicted MACE ($P = .001$) and TVR ($P = .020$), whereas high-risk features predicted death ($P = .027$).

Conclusions Clinical studies report apparently favorable early and midterm results in selected patients with ULM. However, given their limitations in validity and the inherent risk for DES thrombosis, results from randomized trials are still needed to definitely establish the role of DES implantation instead of the reference treatment, surgery. (Am Heart J 2008;155:274-83.)

Coronary artery bypass grafting (CABG) has been considered the standard treatment for significant unprotected left main coronary disease (ULM) since the late 1970s. Percutaneous coronary intervention (PCI) for ULM was attempted as early as 1977 with balloon angioplasty, but the risk of failure was soon recognized.[1] Bare-metal stents (BMSs) later provided important early and midterm

From the [a]Interventional Cardiology, Division of Cardiology, University of Turin, Turin, Italy, [b]Institute of Cardiology, Catholic University, Rome, Italy, [c]Antwerp Cardiovascular Institute Middelheim, AZ Middelheim, Antwerp, Belgium, [d]Institute of Cardiology, University of Ferrara, Ferrara, Italy, [e]Cardiovascular Research Center, Salvatore Maugeri Foundation, IRCCS, Gussago, Italy, [f]Division of Cardiology, Careggi Hospital, Florence, Italy, [g]Cardiology Department, Rangueil Hospital, Toulouse, France, [h]EMO Centro Cuore Columbus, Milan, Italy, [i]Interventional Cardiology Unit, St Raffaele Hospital, Milan, Italy, [j]Division of Cardiovascular Disease, Scripps Clinic, La Jolla, CA, [k]Department of Cardiology, Aarhus University Hospital (Skejby), Aarhus, Denmark, [l]Virginia Commonwealth University Pauley Heart Center, Medical College of Virginia Campus, Virginia Commonwealth University, Richmond, VA, [m]Cardiovascular Research Unit, University of Sheffield, Sheffield, United Kingdom, and [n]Division of Cardiac Surgery, University of Turin, Turin, Italy.

[o]Both authors equally contributed to this work.

Dr Biondi-Zoccai consulted for Boston Scientific, Boston, MA; Cordis, Miami, FL; and Mediolanum Cardio Research, Milan, Italy; and received lecture fees from Bristol-Myers-Squibb, New York, NY. Dr Agostoni has received lecture fees from Cordis.

Submitted April 13, 2007; accepted October 1, 2007.

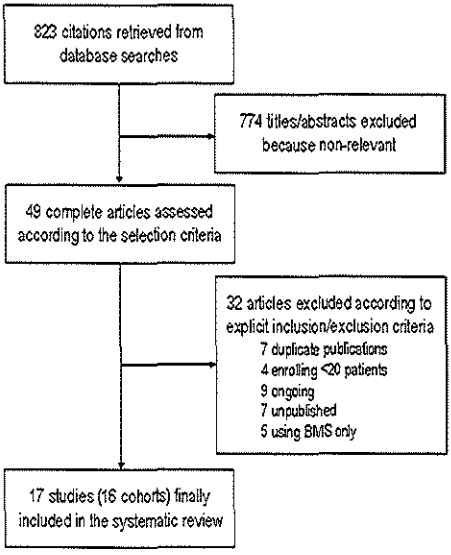
Reprint requests: Giuseppe G.L. Biondi-Zoccai, MD, Division of Cardiology, University of Turin, S. Giovanni Battista-Molinette Hospital, Corso Bramante 88-90, 10126 Turin, Italy.

E-mail: gbiondizoccai@gmail.com

0002-8703/$ - see front matter

doi:10.1016/j.ahj.2007.10.009

Figure 1



Reviewing process.

clinical benefits to the overall group of patients undergoing PCI by reducing periprocedural risks (eg, the need for emergency CABG), restenosis, and target lesion failure; however, the impact of BMS on PCI for ULM has been limited.[2] Drug-eluting stents (DESs) have been introduced into clinical practice in the last few years and proved able to reduce the risk of restenosis.[3] Thus, they hold the promise of improving the outlook of PCI for ULM. Several reports have indeed been published on the short- and midterm results of DES-based PCI for ULM, but most were limited by retrospective nature, small size, and/or single-center design. To thoroughly appraise the risk-benefit balance of percutaneous DES implantation for ULM, in itself and in comparison with BMS-based PCI and CABG, we performed a systematic review and meta-analysis of pertinent studies.

Methods

This review was reported according to established methods,[4] minimizing duplication risks.[5,6] BioMedCentral, clinicaltrials.gov, Google Scholar, and PubMed were searched (January 2000-September 2006),[6] without language restrictions. Citations were screened at title/abstract level and retrieved as full reports. Studies were included if the following criteria applied: (*a*) PCI with stent implantation, (*b*) for ULM disease, (*c*) using DES, and (*d*) in ≥20 patients. Exclusion criteria were as follows: (*a*) duplicate publication, (*b*) ongoing/unpublished study, (*c*) publication only as an abstract or as conference proceedings, (*d*) inclusion of patients not undergoing PCI of the ULM, and (*e*) lack of ≥6-month follow-up.

Table I. Included studies

Study design and first author/study name	Country	Patients treated with DES
Observational cohorts on DES		
Agostoni et al[9]	Netherlands	58
de Lezo et al[15]	Spain	52
Dudek et al[16]	Poland	28
KOMATE[18]	Korea	54
Lozano et al[20]	Spain	42
Migliorini et al[21]*	Italy	156
Price et al[23]	United States	50
Wood et al[25]*	United States	100
Nonrandomized studies of DES versus BMS		
Carrié et al[12]*	France	120
Chieffo et al[10]†	Italy	85
Christiansen et al[14]*	Denmark	46
Han et al[17]	China	138
Park et al[11]	Korea	102
Sheiban et al[24]*	Italy	85
Nonrandomized studies of PCI vs CABG		
Chieffo et al[13]†	Italy	107
Lee et al[19]	United States	50
Palmerini et al[22]	Italy	94

KOMATE, KOrean Multicenter Angioplasty TEam.
*Updated after direct communication with the original investigators.
†Duplicate publication likely or acknowledged.

The primary end point was major adverse cardiovascular events (MACEs), defined as composite of death, nonfatal myocardial infarction, or target vessel revascularization (TVR). The coprimary end point was major adverse cerebrocardiovascular events (MACCEs). Secondary end points were individual components of MACE. Other details on patients, procedures, and study designs were abstracted,[6] and internal validity of included studies was appraised.[7]
All principal investigators of included studies were repeatedly contacted.

Continuous variables are reported as mean (SD) or median (range) and categorical variables as n (%). Pooling was performed according to random-effect models with generic inverse variance weighting with RevMan 4.2 (The Nordic Cochrane Center, København, Denmark) for computing incidence estimates (95% CIs). For nonrandomized controlled comparisons, adjusted risk estimates were pooled after logarithmic transformation according to random-effect models with generic inverse variance weighting. Subgroup,[6] sensitivity, and meta-regression analyses[8] were performed to appraise robustness and explore moderators (SPSS 11.0; SPSS, Chicago, IL). Statistical heterogeneity was appraised with I^2 and small study bias with funnel plots and regression analysis. Unadjusted P values are reported throughout, with hypothesis testing set at the 2-tailed .05 level.

Results

From 823 initial citations (Figure 1), we excluded 806 hits, leaving 17 studies,[9-25] (Tables I and II). The 17 included studies reported on a total of 16 nonduplicate cohorts, enrolling 1278 subjects undergoing PCI with DES for ULM disease. Eight studies were observational reports on 540 patients treated with

Table II. Major excluded studies

Study	Country	Patients	Design	Reason for exclusion
Arampatzis et al (2003)	Netherlands	31	Observational cohort	Duplicate publication
Arampatzis et al (2004)	Netherlands	16	Observational cohort	Duplicate publication
Berenguer et al (2005)	Spain	7	Observational cohort	Duplicate publication
CARDIA (2006)	UK	600	RCT of PCI vs CABG	Ongoing
COMBAT	Worldwide	1800	RCT of PCI vs CABG	On hold
eCYPHER (2006)	Worldwide	171	Observational cohort	Unpublished
Erglis et al	Europe	103	RCT of DES vs BMS	Unpublished
European Registry	Europe	224	Observational cohort	Unpublished
French Multicenter Taxus Study	France	150	Observational cohort	Ongoing
Herz et al (2005)	Israel	4	Non-RCT of PCI vs CABG	<20 Patients included
Kim et al (2006)	Korea	116	Observational cohort	Duplicate publication
Korean Randomized Study	Korea	124	RCT of PCI vs CABG	Ongoing
LE MANS (2005)	Poland	37	Observational cohort	Unpublished
Lefevre et al	France	146	Observational cohort	Unpublished
Leipzig Study	Germany	200	RCT of PCI vs CABG	Ongoing
Lopez-Palop et al (2004)	Spain	10	Observational cohort	<20 Patients included
Munich Study	Germany	340	RCT of CYPHER vs Taxus	Ongoing
Palmerini et al (2005)	Italy	42	Observational cohort	Duplicate publication
Peszek-Przybyla et al (2006)	Poland	62	Observational cohort	<20 Patients included
Pohl et al (2004)	Germany	23	RCT of PCI vs CABG	BMS use only
REVASCULARIZE	United States	NA	RCT of PCI vs CABG	Ongoing
SECURE	United States	20	Observational cohort	Unpublished
SYNTAX	Worldwide	1500	RCT of PCI vs CABG	Ongoing
Teplitsky et al (2004)	Israel	11	Observational cohort	<20 Patients included
TRUE	Europe	115	Observational cohort	Unpublished
Valgimigli et al (2005)	Netherlands	80	Before-after study	Duplicate publication
Valgimigli et al (2006)	Netherlands	110	Observational cohort	Duplicate publication

References are available from the corresponding author upon request. *NA*, Not available or applicable; *RCT*, randomized clinical trial.

DES,[9,15,16,18,20,21,23,25] 6 studies were nonrandomized comparisons of PCI with DES (n = 576) versus BMS (n = 509),[10-12,14,17,24] and 3 were nonrandomized comparisons of PCI with DES (n = 251) versus CABG (n = 419).[13,22,23] Median follow-up was 10 months (range 6-19 months). The overall internal validity of all included studies was only moderate, given the presence of several potential threats to study quality. Details on included studies are available in Tables III and IV.

All studies provided enough details on the primary end point (ie, MACE or MACCE); however, incomplete reporting of other events was common (Table V). Overall analysis (Figures 2 and 3) showed inhospital death in 2.3% (1.1-3.4, I^2 = 7.4%) and inhospital myocardial infarction in 2.5% (1.2-3.8, I^2 = 27%). Overall midterm follow-up showed MACE in 16.5% (11.7-21.3, I^2 = 84%), death in 5.5% (3.4-7.7, I^2 = 64%), and TVR in 6.5% (3.7-9.2, I^2 = 80%). Comparing MACE in studies limiting follow-up to 6 months[14,18,19,21,22] versus those extending follow-up to >6 months[9-13,15-17,20,23-25] showed rates of, respectively, 14.2% (5.4-23.0, I^2 = 85%) and 17.7% (11.7-23.8, I^2 = 86%).

Multivariable adjusted estimates for DES vs BMS were reported only by a handful of studies,[10,12,24] for a total of 206 patients treated with DES versus 190 with BMS (Figure 4). Pooled analysis showed the superiority of DES both in follow-up MACE and TVR (respectively, odds ratio [OR] = 0.34 [0.16-0.71], P = .004, I^2 = 45.3%, and OR = 0.34 [0.12-0.94], P = .04, I^2 = 0%).

Adjusted estimates for the DES-based PCI versus CABG were reported only by Chieffo et al[13] and Lee et al,[19] for a total of 157 patients treated with DES and 265 with CABG (Figure 4). Meta-analysis for the occurrence of MACCE at follow-up suggested the superiority of DES versus CABG (OR = 0.46 [0.24-0.90], P = .02, I^2 = 0%), even if this estimate should be viewed with caution, given the small number of patients included, the width of the ICs, and the caveats on the internal validity of included studies.

Subgroup analyses were performed for (*a*) DES implantation for nonbifurcational ULM, (*b*) DES implantation for ULM in low-risk patients, and (*c*) DES implantation for ULM in high-risk subjects. Given the limited details provided by the individual studies on these subgroups despite repeated efforts to contact the primary authors, computations performed on the available data are hereby reported as exploratory findings only.

Including a recent update from a multicenter registry and excluding duplicate sources, a total of 285 patients with nonbifurcational ULM and treated with DES had detailed follow-up data.[9,11,14,15,21,24-26] Pooled analysis showed inhospital death in 0.9% (0%-2.1%, I^2 = 0%) and myocardial infarction in 3.2% (0%-5.6%, I^2 = 0%),

Table III. Characteristics of included studies

Study	Age (y)	Male (%)	Diabetic (%)	ACS (%)	Nonbifurcational ULM (%)	Surgical high-risk features (%)*	LVEF (%)	COPD (%)	RF (%)	Angiographic follow-up (%)	Oral antiplatelet regimen†	SES/ PES use (%)
Agostoni et al[9]	63 ± 13	69	33	32	45	NA	48 ± 12	NA	NA	NA	A + C, 6 m	NA
Carrié et al[12]	66 ± 12	75	29	63	0	NA	59 ± 11	NA	NA	100	A + C, 6m	0/100
Chieffo et al[10]	63 ± 12	84	21	31	19	45	51 ± 11	NA	NA	85	A + C, ≥6 m	NA
Chieffo et al[13]	64 ± 10	NA	19	32	19	32	52 ± 10	NA	6	85	NA	51/49
Christianson et al[14]	NA	NA	NA	NA	46	43	NA	NA	NA	NA	A + C, ≥3 m	NA
de Lezo et al[15]	63 ± 11	42	35	83	58	NA	57 ± 13	NA	NA	67	A + C, 12 m	100/0
Dudek et al[16]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	A + C, 6-12 m	46/54
Han et al[17] ‡	62 ± 11	NA	29	45	29	NA	NA	NA	NA	36	A + C, 6-9 m	NA
KOMATE[18]	59 ± 9	68	27	65	67	NA	60 ± 18	NA	4	44	A + C, 6 m	65/35
Lee et al[19]	72 ± 15	50	36	66	40	64	51 ± 15	NA	16	42	A + C, 6 m	84/16
Lozano et al[20]	70 ± 11	60	33	17	31	100	37‡	NA	NA	57	A + C, 3-6 m	71/19
Migliorini et al[21]	70 ± 10	80	32	69	15	61	27§	NA	27	84	A + C, 6 m	26/74
Palmerini et al[22]	73 ± 11	70	26	63	20	64	52 ± 14	16	20	66	NA	68/32
Park et al[11]	60 ± 11	75	28	60	29	NA	60 ± 8	NA	NA	84	A + C, 6 m‖	100/0
Price et al[23]	69 ± 13	64	26	34	6	58	24¶	NA	16	98	A + C, indefinitely	100/0
Sheiban[24]	68 ± 10	77	22	67	40	46	55 ± 10	NA	4	61	A + C or A + T, 6 m	100/0
Wood et al[25]	68 ± 13	64	30	NA	31	NA	47 ± 13	NA	NA	NA	A + C, ≥6 m	NA

ACS, Acute coronary syndrome; LVEF, left ventricular ejection fraction; COPD, chronic pulmonary obstructive disease; RF, renal failure; SES, sirolimus-eluting stent (of all DESs); PES, paclitaxel-eluting stent (of all DESs).

**Proportion with LVEF ≤40%.*

† A stands for aspirin, C for clopidogrel, and T for ticlopidine, followed by duration in months of dual antiplatelet therapy.

‡ Patients with ejection fraction (LVEF) ≤45%.

§ Proportion with LVEF ≤35%.

‖ Cilostazol was also administered for 1 month after the procedure.

¶ Defined as EuroSCORE ≥6 or Parsonnet score ≥15.

whereas after a median follow-up of 10 months, MACE occurred in 14.7% (6.2%-23.2%, I^2 = 75%), death in 4.1% (1.7%-6.6%, I^2 = 0%), and TVR in 6.7% (0.9%-12.4%, I^2 = 64%). Available studies reported on a total of 260 patients with surgical low-risk features (European System for Cardiac Operative Risk Evaluation <6 or Parsonnet score <15).[10,14,21,24] Meta-analysis showed inhospital death in 3.0% (0%-6.1%, I^2 = 0%) and myocardial infarction in 3.0% (0.1%-6.0%, I^2 = 0%), whereas after 8 months, MACE occurred in 15.7% (7.7%-23.7%, I^2 = 74%), death in 4.8% (1.6%-8.0%, I^2 = 0%), and TVR in 8.5% (1.9%-15.1%, I^2 = 77%). Conversely, detailed event rates were available for 312 patients with surgical high-risk features (European System for Cardiac Operative Risk Evaluation ≥6 or Parsonnet score ≥15).[10,14,20,21,24] Random-effect quantitative pooling yielded inhospital death in 6.6% (3.6%-9.7%, I^2 = 0%) and myocardial infarction in 1.3% (0%-3.0%, I^2 = 0%), whereas after 8 months, MACE occurred in 20.6% (11.9%-29.2%, I^2 = 75%), death in 12.0% (7.5%-16.6%, I^2 = 26%), and TVR in 6.4% (0.7%-12.1%, I^2 = 77%).

Weighted least squares meta-regression disclosed a highly statistically significant interaction between the rate of nonbifurcational ULM and the risk of MACE

Table IV. Internal validity of included studies

Study	Prospective design	Multicenter enrolment	Selection bias	Performance bias	Attrition bias	Detection bias	Multivariable adjustment for potential confounders
Agostoni et al[9]	No	No	B	B	D	B	Probably adequate
Carrié et al[12]	Yes	No	B	B	A	B	Probably adequate
Chieffo et al[10]	No	Yes	B	B	A	B	Probably adequate
Chieffo et al[13]	No	No	B	B	A	B	Probably adequate
Christiansen et al[14]	Yes	No	C	B	D	B	None reported
de Lezo et al[15]	No	Yes	B	B	A	B	None reported
Dudek et al[16]	Unclear	No	B	B	D	B	None reported
Han et al[17]	No	No	C	B	C	B	None reported
KOMATE[18]	Unclear	Yes	B	B	C	C	None reported
Lee et al[19]	No	No	B	B	D	B	Probably adequate
Lozano et al[20]	Yes	Yes	B	B	B	C	None reported
Migliorini et al[21]	No	No	B	B	B	B	Probably adequate
Palmerini et al[22]	Yes	No	B	B	C	C	None reported
Park et al[11]	No	No	B	B	A	C	None reported
Price et al[23]	No	No	B	B	A	B	Probably adequate
Sheiban et al[24]	No	No	B	B	A	B	Probably adequate
Wood et al[25]	No	No	B	B	A	B	None reported

Risk of bias is expressed as A (low), B (moderate), C (high), or D (incomplete reporting).

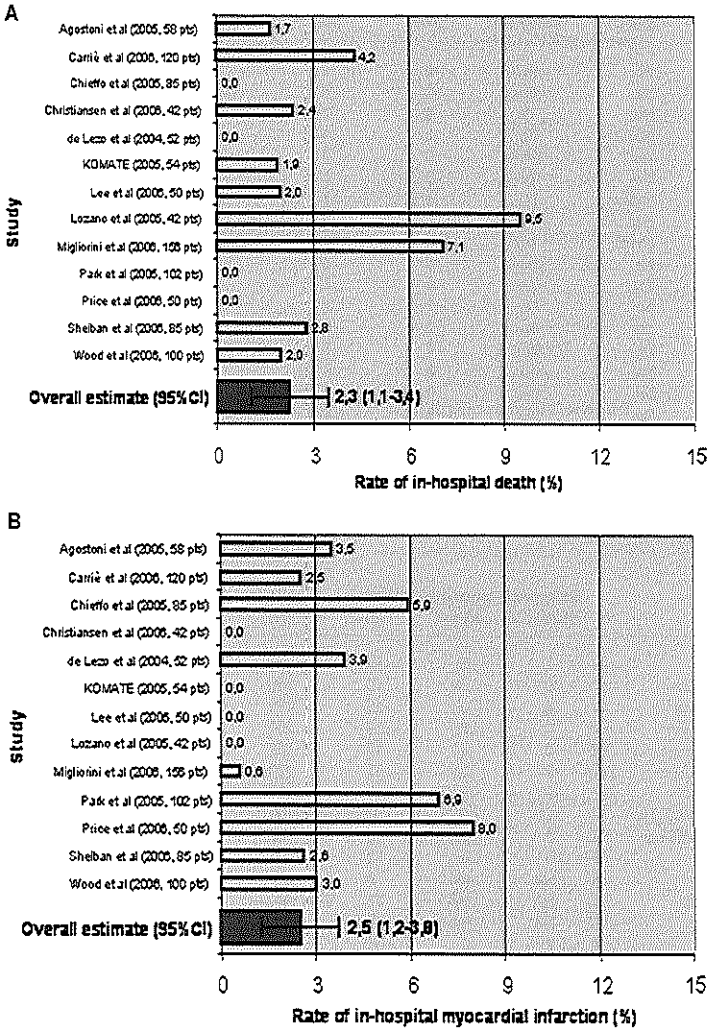
Table V. Unadjusted clinical outcomes

Study	N	Inhospital death (%)	Inhospital MI (%)	Follow-up (m)	Follow-up completion (%)	MACE (%)	MACCE (%)	Death (%)	MI (%)	Stroke (%)	TVR (%)	ST (%)
Agostoni et al[9]	58	2	3	14	100	16	NA	5	3	NA	7	NA
Carrié et al[12]–BMS arm*	57	0	5	10	100	66	NA	7	5	NA	26	0
Carrié et al[12]–DES arm*	49	4	3	10	100	13	13	10	3	0	2	1
Chieffo et al[10]–BMS arm	64	0	8	12	100	42	NA	14	NA	NA	30	0
Chieffo et al[10]–DES arm	85	0	6	12	100	25	NA	4	NA	NA	19	1
Chieffo et al[13]–CABG arm	142	2	26	12	100	42	44	8	27	2	6	NA
Chieffo et al[13]–DES arm	107	0	9	12	100	33	34	3	10	1	20	1
Christiansen et al[14]–BMS arm*	39	31	3	6	100	44	44	31	5	0	8	NA
Christiansen et al[14]–DES arm*	42	2	0	6	100	7	7	5	2	0	5	2
de Lezo et al[15]	52	0	4	12	100	6	NA	0	4	NA	2	0
Dudek et al[16]	36	NA	NA	9	NA	14	NA	NA	NA	NA	0	NA
Han et al[17]–BMS arm	34	NA	NA	12	NA	27	NA	9	3	NA	15	NA
Han et al[17]–DES arm	138	NA	NA	12	NA	11	NA	7	1	NA	10	NA
KOMATE[18]	54	2	0	6	81	5	NA	2	0	NA	2	0
Lee et al[19]–CABG arm	123	5	2	6	NA	14	17	11	2	8	1	NA
Lee et al[19]–DES arm	50	2	0	6	NA	11	11	4	4	0	7	0
Lozano et al[20]	42	10	0	10	100	26	NA	20	4	NA	2	1
Migliorini et al[21]*	156	7	1	6	100	24	24	11	1	0	12	0
Palmerini et al[22]–CABG arm	154	NA	NA	6	NA	14	NA	11	13	NA	NA	NA
Palmerini et al[22]–DES arm	94	NA	NA	6	NA	22	NA	9	13	NA	NA	NA
Park et al[11]–BMS arm	121	0	8	12	100	25	NA	0	8	NA	17	0
Park et al[11]–DES arm	102	0	7	12	100	9	NA	0	7	NA	2	0
Price et al[23]	50	0	8	8	100	54	NA	10	10	NA	44	4
Sheiban et al[24]–BMS arm*	69	10	3	10	99	36	36	20	3	0	13	0
Sheiban et al[24]–DES arm*	77	3	3	10	100	9	10	3	3	1	4	0
Wood et al[25]*	100	2	3	19	100	19	NA	6	3	NA	7	1

MI, Myocardial infarction; *ST*, stent thrombosis.
*Updated after communication with investigators.

(β = −0.015 [−0.008 to −0.022], P = .001) (Figure 5). Intriguingly, location of ULM disease could explain as much as 58% of the observed variability (R^2 = 0.61, adjusted R^2 = 0.58). The prevalence of high-risk features proved to be a statistically significant predictor of midterm follow-up case fatality (β = 0.017 [0.003-

Figure 2



Overall risk of inhospital death (**A**) and myocardial infarction (**B**) in patients treated with DESs for ULM.

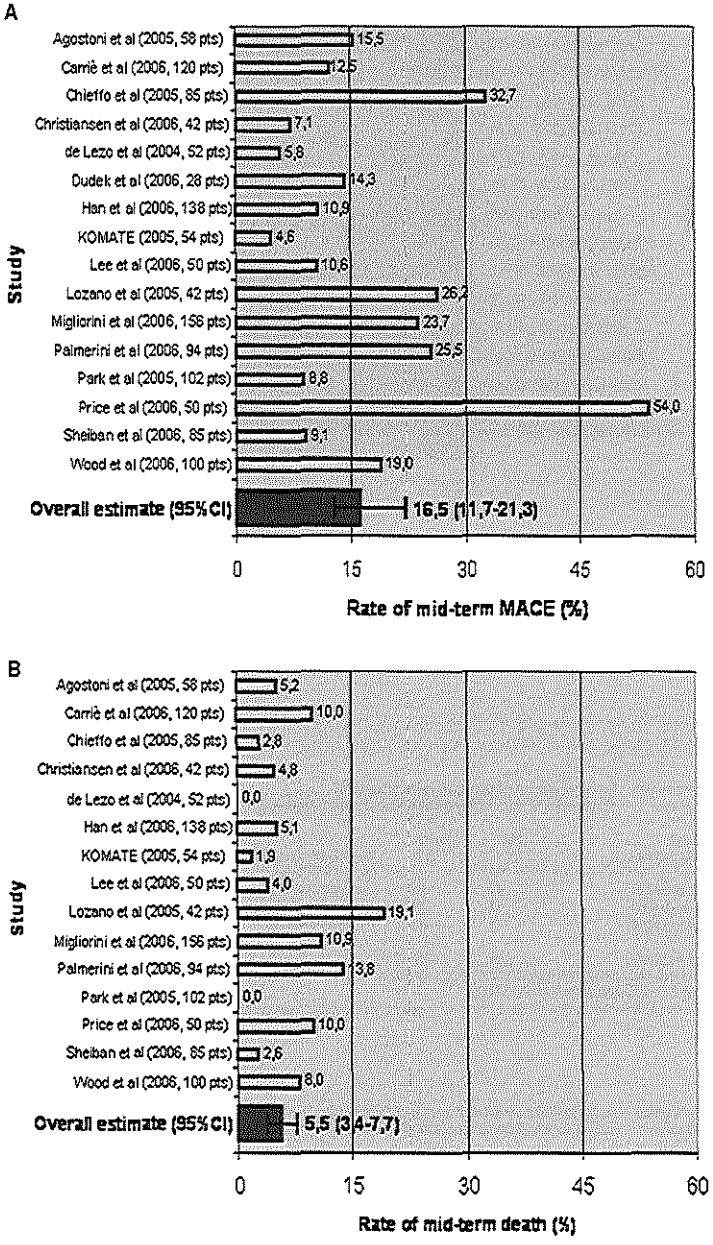
0.031], $P = .027$, $R^2 = 0.58$, adjusted $R^2 = 0.51$) but not of midterm MACE ($P = .55$). On the other hand, TVR was significantly associated with the rate of nonbifurcational ULM ($\beta = -0.016$ [−0.003 to −0.030], $P = .020$). Angiographic follow-up rate, despite being a common cause of event inflation in coronary intervention studies,[27] was not significantly associated with MACE or TVR.

Sensitivity analyses conducted with fixed-effect, and DerSimonian-Laird methods confirmed the findings of the original analyses. Testing for small study bias showed no statistical significance ($P = .65$).

Discussion

The present meta-analysis, reporting on DES implantation for ULM, has the following implications: published reports on DES use now include >1200 subjects, confirming that this treatment option has been already adopted into clinical practice despite the lack of a sound

Figure 3



Overall risk of MACEs (**A**), death (**B**), and TVR (**C**) at a median follow-up of 10 months (range 6-19 months) in patients treated with DESs for ULM.

evidence base; although overall results suggest an apparently favorable risk of MACE in selected patients, most studies are fraught with validity threats; moreover, clinical follow-up is to date still limited at the midterm threshold; thus, results from randomized trials comparing percutaneous versus surgical revascularization are still

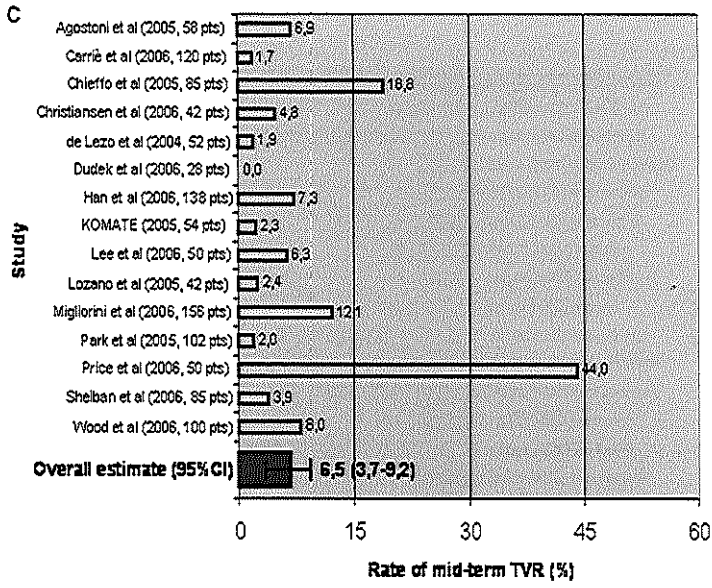
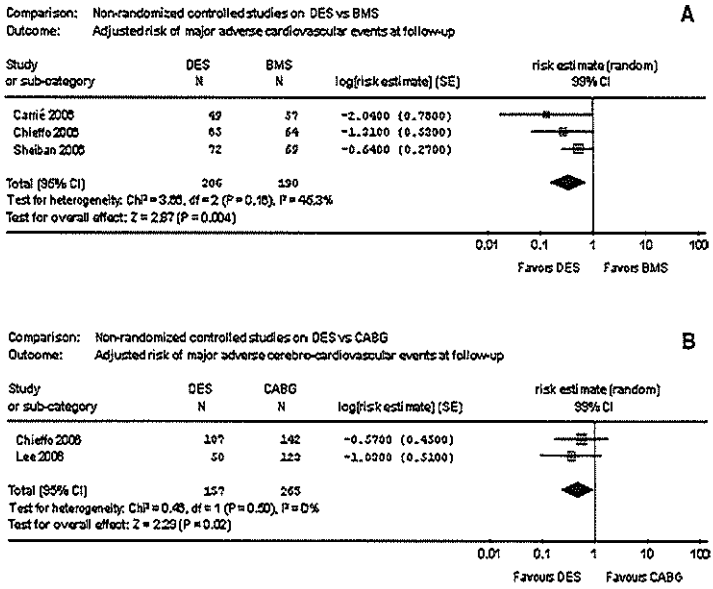


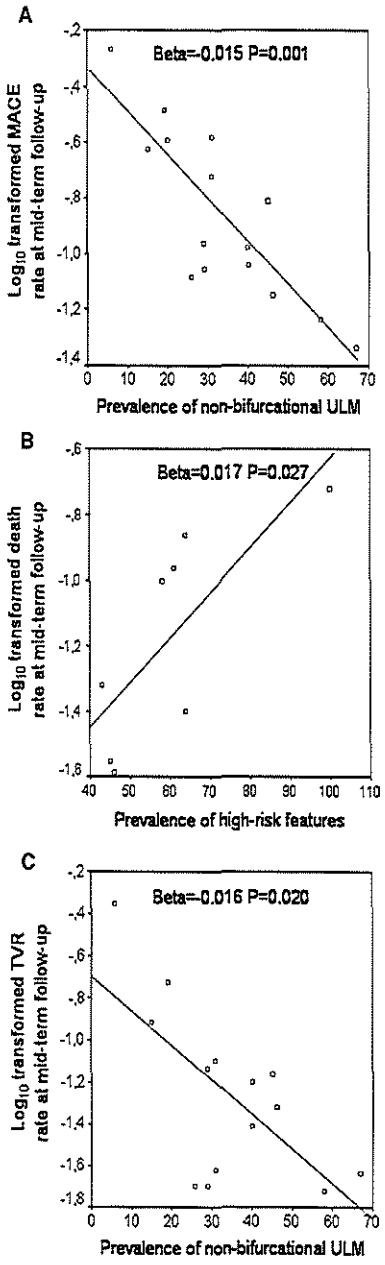
Figure 3 (continued)

Figure 4



Forest plots for the adjusted comparisons between DESs versus BMSs (**A**) or DES versus bypass surgery (CABG) in patients with ULM (**B**).

Figure 5



L'Abbé plots for the association between prevalence of nonbifurcational ULM and rate of midterm follow-up MACEs) (**A**); prevalence of high-risk features and midterm follow-up death (**B**); and prevalence of high-risk features and midterm TVR (**C**).

needed to establish the role of percutaneous DES implantation in the evidence-based medicine hierarchy in comparison with the reference treatment, surgery, especially given the recent concerns raised on late stent thrombosis.[28]

Unprotected left main disease occurs in 5% of patients undergoing coronary angiography[29] and has been, for decades, a strict indication for CABG. Since DES approval,[3] interventionists have begun to use them not only in patients with ULM at very high surgical risk but also in those with more favorable characteristics.[30] Most reports were, however, small single-center experiences, with obvious limitations in external validity. The available evidence on patient selection and risk stratification in patients undergoing PCI with DES for ULM has already established that nonbifurcational ULM is associated with a more favorable prognosis than distal (ie, bifurcation) ULM, but whether surgery should be the first-line treatment even for nonbifurcational ULM remains debated.[26] Recent data have lead to an overall reappraisal of the long-term safety of DES,[31] given the likely increase in stent thrombosis, and this has had even greater implications on DES-based PCI for ULM.

Notwithstanding the limitations of included studies, we aimed to provide a comprehensive synthesis of the evidence on DES for ULM. We identified several studies, including registries or nonrandomized comparison of DES versus BMS or CABG, but no randomized trials. Pooled analyses of registry data from the present work, including >1200 patients, support the early and midterm safety of DES implantation, especially in carefully selected patients and under the premise that PCI is performed by experienced operators in centers with on-site surgical backup. The beneficial impact of DES over BMS in these lesions is clearly and unanimously shown in the available controlled studies. Indeed, in-stent restenosis has been called into question as a potential cause of acute coronary syndromes in unspecified lesions, but in ULM restenosis, it is well known as a potential cause of sudden cardiac death or myocardial infarction. Thus, the antiproliferative action of DES is of paramount importance in ULM lesions, and to date, DES should likely be recommended whenever PCI for ULM is envisioned. Nonetheless, our findings on DES in general, and on the comparison with CABG in particular, should be viewed in light of the need to wait for the long-term results of ad hoc randomized trials (eg, COMBAT, SYNTAX, and REVASCULARIZE studies) before drawing any definitive conclusion.

Among the limitations of this work, drawbacks of systematic reviews of nonrandomized studies are well known, and this type of meta-analysis is obviously inferior to randomized controlled trials in the evidence hierarchy.[4] More specific limits of this work include the extent of statistical inconsistency, the differences in patients and techniques among different centers, the lack

of data on MACE for the PCI versus CABG comparison, and the frequent limitations in included studies, which should be strongly borne in mind and prompt the design and conduction of more rigorous observational as well as randomized studies.

We thank original authors for their help. This study is part of a training project of the Meta-analysis and Evidence-based Training in Cardiology Center, Turin, Italy (http://www.metcardio.org).

References

1. Meier B. The first coronary angioplasties in Zurich. In: Bertrand M, editor. The evolution of cardiac catheterization and interventional cardiology. St Albans, UK: Iatric Press; 2006. p. 61-74.
2. Takagi T, Stankovic G, Finci L, et al. Results and long-term predictors of adverse clinical events after elective percutaneous interventions on unprotected left main coronary artery. Circulation 2002;106:698-702.
3. Hill RA, Dundar Y, Bakhai A, et al. Drug-eluting stents: an early systematic review to inform policy. Eur Heart J 2004;25:902-19.
4. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.
5. Biondi-Zoccai GG, Lotrionte M, Abbate A, et al. Compliance with QUOROM and quality of reporting of overlapping meta-analyses on the role of acetylcysteine in the prevention of contrast associated nephropathy: case study. BMJ 2006;332:202-9.
6. Meta-analysis and Evidence-based Training in Cardiology Center protocol #1-2006. Available at: http://www.metcardio.org/protocols.html [last accessed on July 10, 2007].
7. The Cochrane Collaboration handbook for systematic reviews of interventions. Available at: http://www.cochrane.org/resources/handbook/ [last accessed on July 10, 2007].
8. Biondi-Zoccai GG, Abbate A, Agostoni P, et al. Long-term benefits of an early invasive management in acute coronary syndromes significantly depend on intracoronary stenting and aggressive antiplatelet treatment: a metaregression. Am Heart J 2005;149:504-11.
9. Agostoni P, Valgimigli M, Van Mieghem CA, et al. Comparison of early outcome of percutaneous coronary intervention for unprotected left main coronary artery disease in the drug-eluting stent era with versus without intravascular ultrasonic guidance. Am J Cardiol 2005;95:644-7.
10. Chieffo A, Stankovic G, Bonizzoni E, et al. Early and mid-term results of drug eluting stent implantation in unprotected left main. Circulation 2005;111:791-5.
11. Park SJ, Kim YH, Lee BK, et al. Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis: comparison with bare metal stent implantation. J Am Coll Cardiol 2005;45:351-6.
12. Carrié D, Lhermusier T, Hmem M, et al. Clinical and angiographic outcome of paclitaxel-eluting stent implantation for unprotected left main coronary artery bifurcation narrowing. EuroIntervention 2006;1:396-402.
13. Chieffo A, Morici N, Malsano F, et al. Percutaneous treatment with drug-eluting stent implantation versus bypass surgery for unprotected left main stenosis. A single-center experience. Circulation 2006;113:2542-7.
14. Christiansen EH, Lassen JF, Andersen HR, et al. Outcome of unprotected left main percutaneous coronary intervention in surgical low-risk, surgical high-risk, and acute myocardial infarction patients. EuroIntervention 2006;1:403-8.
15. de Lezo JS, Medina A, Pan M, et al. Rapamycin-eluting stents for the treatment of unprotected left main coronary disease. Am Heart J 2004;148:481-5.
16. Dudek D, Heba G, Giszterowicz D, et al. Stenting of unprotected left main coronary artery in patients with low preoperative risk of coronary artery bypass grafting. Kardiol Pol 2006;64:929-36.
17. Han YL, Wang SL, Jin QM, et al. Efficacy of stenting for unprotected left main coronary artery disease in 297 patients. Chin Med J (Engl) 2006;119:544-50.
18. Lee SH, Ko YG, Jang Y, et al, for the Korean Multicenter Angioplasty Team (KOMATE) Investigators. Sirolimus- versus paclitaxel-eluting stent implantation for unprotected left main coronary artery stenosis. Cardiology 2005;104:181-5.
19. Lee MS, Kapoor N, Jamal F, et al. Comparison of coronary artery bypass surgery with percutaneous coronary intervention with drug-eluting stents for unprotected left main coronary artery disease. J Am Coll Cardiol 2006;47:864-70.
20. Lozano I, Herrera C, Moris C, et al. Drug-eluting stents in patients with left main coronary lesions who are not candidates for surgical revascularization. Rev Esp Cardiol 2005;58:145-52.
21. Migliorini A, Moschi G, Giurlani L, et al. Drug-eluting stent supported percutaneous coronary intervention for unprotected left main disease. Catheter Cardiovasc Interv 2006;68:225-30.
22. Palmerini T, Marzocchi A, Marrozzini C, et al. Comparison between coronary angioplasty and coronary artery bypass surgery for the treatment of unprotected left main coronary artery stenosis (the Bologna Registry). Am J Cardiol 2006;98:54-9.
23. Price MJ, Cristea E, Sawhney N, et al. Serial angiographic follow-up of sirolimus-eluting stents for unprotected left main coronary artery revascularization. J Am Coll Cardiol 2006;47:871-7.
24. Sheiban I, Moliga E, Moretti C, et al. Sirolimus-eluting stents vs bare metal stents for the treatment of unprotected left main coronary artery stenosis. EuroIntervention 2006;2:356-62.
25. Wood F, Bazemore E, Schneider JE, et al. Technique of left main stenting is dependent on lesion location and distal branch protection. Catheter Cardiovasc Interv 2005;65:499-503.
26. Chieffo A, Park SJ, Valgimigli M, et al. Favorable long-term outcome after drug-eluting stent implantation in nonbifurcation lesions that involve unprotected left main coronary artery. A multicenter registry. Circulation 2007;116:158-62.
27. Ruygrok PN, Melkert R, Morel MA, et al. Does angiography six months after coronary intervention influence management and outcome? BENESTENT II Investigators. J Am Coll Cardiol 1999;34:1507-11.
28. Bavry AA, Kumbhani DJ, Helton TJ, et al. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. Am J Med 2006;119:1056-61.
29. Giannoglou GD, Antoniadis AP, Chatzizisis YS, et al. Prevalence of narrowing > or = 50% of the left main coronary artery among 17,300 patients having coronary angiography. Am J Cardiol 2006;98:1202-5.
30. Huang HW, Brent BN, Shaw RE. Trends in percutaneous versus surgical revascularization of unprotected left main coronary stenosis in the drug-eluting stent era—a report from the American College of Cardiology–National Cardiovascular data registry (ACC-NCDR). Catheter Cardiovasc Interv 2006;68:867-72.
31. Biondi-Zoccai GGL, Agostoni P, Moretti C, et al. Making sense of the recent meta-analytical confusion concerning the safety of drug-eluting stents. EuroIntervention 2007 [in press].

PART 2

INTERVENTION FOR CHRONIC TOTAL OCCLUSIONS

CHAPTER 10

CHRONIC TOTAL OCCLUSION TREATMENT IN POST-CABG PATIENTS: SAPHENOUS VEIN GRAFT VERSUS NATIVE VESSEL RECANALIZATION-LONG-TERM FOLLOW-UP IN THE DRUG-ELUTING STENT ERA

Chronic Total Occlusion Treatment in Post-CABG Patients: Saphenous Vein Graft Versus Native Vessel Recanalization—Long-term Follow-up in the Drug-Eluting Stent Era

Emanuele Meliga, MD, Héctor M. García-García, MD, MSc, Neville Kukreja, MRCP, Joost Daemen, MD, Shuzou Tanimoto, MD, Steve Ramcharitar, MD, PhD, Carlos A.G. van Mieghem, MD, Georgios Sianos, MD, Martin van der Ent, MD, PhD, Willem J. van der Giessen, MD, PhD, Pim de Feyter, MD, PhD, Ron van Domburg, PhD, and Patrick W. Serruys,* MD, PhD

Objective: To compare the postprocedural and long-term clinical outcomes of two groups of patients, all presenting with chronic saphenous vein graft (SVG) occlusion, who underwent either SVG or native vessel reopening. Background: Chronic total occlusions (CTO) treatment in patients who underwent previous surgical revascularization is a dilemma and the choice of performing native vessel or SVG recanalization is not always easy. Methods: Between July 2002 and October 2004, a total of 260 patients were successfully treated for a CTO. Of them, we selected all patients (n = 24) who had previous bypass surgery with graft occlusion. Of this final group, 13 patients underwent a percutaneous graft recanalization while 11 underwent native vessel reopening. Results: Primary end points were in-hospital and 3-year rates of death, myocardial infarction, target lesion revascularization, and target vessel revascularization. No events occurred in either group during the in-hospital period. Cumulative 3-year event-free survival in the native vessel and SVG group was 81.8% and 83.9% respectively (P = NS). One death and one TVR occurred in each group. Conclusion: In selected cases, SVG reopening instead of the native vessel is feasible. In such a high-risk population, drug-eluting stent implantation in both SVG and native CTO lesions is associated with good long-term outcomes.

Key words: percutaneous coronary intervention; total occlusions; bypass grafts; coronary

INTRODUCTION

Chronic total occlusions (CTOs) remain one of the most challenging problems for interventionists as the procedural success rate and acute outcome are still relatively poor [1–6]. Percutaneous treatment of saphenous vein grafts (SVGs) occlusions, notwithstanding the use of drug-eluting stent (DES) and new protection devices, remains exacting [7]; the atherosclerotic disease in SVGs is pathologically different from the native vessel, showing soft and friable lesions usually with a poorly developed fibrous cap and large and bulky thrombi that tend to occupy the entire length of the graft [8–12]. Which revascularization treatment should we then recommend to patients with chronic SVG occlusions? Is it worthwhile to treat the SVG occlusions or should we avoid this approach and always attempt to treat the native bypassed coronary arteries?

To clarify this issue better we compared the clinical outcomes of two groups of patients, all presenting

Interventional Cardiology Department, Thoraxcenter, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands

*Correspondence to: Prof. P.W. Serruys, MD, PhD, Thoraxcenter, Ba-583, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl

Received 12 October 2006; Revision accepted 20 December 2006

DOI 10.1002/ccd.21100
Published online 22 June 2007 in Wiley InterScience (www.interscience.wiley.com).

chronic SVG occlusion, who underwent either SVG or native vessel reopening.

METHODS

Population

Demographic and procedural data regarding all patients undergoing PCI at our centre were prospectively entered into a dedicated database. Between July 2002 and October 2004, a total of 351 patients had a CTO treatment attempt in our center; 260 were successfully treated (74.1%). Of them, we retrospectively selected only those patients ($n = 24$) who had undergone previous saphenous vein bypass grafting and subsequently had total occlusion of one or more grafts. Of this final group, 13 patients underwent a percutaneous reopening treatment on the occluded graft while 11 underwent percutaneous reopening of the native vessel (Table I).

Exclusion criteria were unsuccessful attempt and intolerance or contraindication to clopidogrel. No other predefined clinical inclusion or exclusion criteria were considered, and the indication for PCI was decided on clinical and angiographic characteristics.

End Points

The primary outcome measures investigated were the occurrences of death, myocardial infarction (MI), target vessel revascularization (TVR), target lesion revascularization (TLR), and major adverse cardiac events (MACE) defined as a nonhierarchical composite of all cause death, nonfatal MI, or repeat revascularization during hospital stay and at 3 years.

Definitions

CTO was defined as a complete coronary obstruction (TIMI flow grade 0) with an estimated duration of >3 months. Technical success was defined as the ability to cross and open the occluded segment with no more than 40% residual stenosis in all views; procedural success was defined as a technical success with no in-hospital MACE. MI was defined as a threefold CK-MB increase; hemodynamic instability was defined as the occurrence of sustained ventricular arrhythmias or prolonged hypotension (BP < 90/60 mm Hg). TLR was defined as any revascularization performed on the treated segment; TVR was defined as any reintervention performed on the treated vessel.

Interventional Technique

The operators performed the procedure according to standard techniques of the time via the femoral or brachial approach. All procedural and technical details and the choice of devices were left to the operator's judgment. In the cardiac catheterization laboratory, patients received a bolus of 10.000 units of heparin followed by repeated boluses per a weight-based protocol to achieve an activated clotting time >250 sec. All the lesions were treated with DES implantation. Periprocedural abciximab was administered at the operator's discretion. After the procedure, clopidogrel (75 mg daily) was prescribed to all patients for 6 months after stent implantation; aspirin was given indefinitely.

TABLE I. Baseline Clinical Characteristics

	SVG group ($N = 11$)	Native group ($N = 13$)	P value
Age (years)	67.8 ± 12.4	60.8 ± 10.9	NS
Women, n (%)	1 (7.6)	2 (18.1)	NS
Diabetes mellitus, n (%)	5 (38.4)	3 (27.2)	NS
Hypertension, n (%)	7 (53.8)	4 (36.6)	NS
Current smoking, n (%)	2 (15.3)	2 (18.1)	NS
Familiarity, n (%)	7 (53.8)	6 (54.5)	NS
Dislipidemia, n (%)	10 (76.9)	9 (81.1)	NS
Prior myocardial infarction, n (%)	7 (53.8)	6 (54.5)	NS
Prior PCI, n (%)	5 (38.4)	7 (63.6)	NS
Clinical presentation (ACS), n (%)	6 (46.1)	1 (9)	<0.05

SVG, saphenous vein graft; PCI, percutaneous coronary intervention; ACS, acute coronary syndrome.

Follow-up

A follow-up visit or telephone interview was scheduled at 30 days, 6 months, 1 year, and then yearly. Civil registries were queried in case of death, to determine whether it was or not a cardiac death. A health questionnaire was subsequently sent to all living patients with specific questions on rehospitalization and MACE [13,14]. All repeat interventions and rehospitalizations were prospectively collected during follow-up and entered into a dedicated database. An exercise tolerance test was recommended after 6 months in event-free patients; angiographic follow-up was performed only in those patients with recurrence of symptoms or with a positive stress test.

Statistical Analysis

Variables with normal distribution were analyzed using parametric tests while variables with a non-normal distribution were analyzed with nonparametric tests. Continuous variables are expressed as mean ± SD or median ± SD and differences were compared using Student's t test or Mann–Whitney test. Categorical variables are expressed as counts and percentages; differences were assessed by Fisher's exact test or χ^2 test, as appropriate. All statistical tests were two-tailed. When more than one clinical event occurred in a patient, all the events occurring were considered for survival analysis. All analyses were performed using SPSS version 12 statistical software (SPSS Inc., Chicago, IL). A P value < 0.05 was considered significant.

Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.
Published on behalf of The Society for Cardiovascular Angiography and Interventions (SCAI).

TABLE II. Angiographic and Procedural Characteristics

	SVG group ($N = 11$)	Native group ($N = 13$)	P value
Three vessel disease, n (%)	13 (100)	7 (63.6)	<0.05
TL location, n (%)			
LAD	2 (15.3)	0 (0)	NS
LCX	4 (30.7)	7 (63.6)	NS
RCA	7 (53.8)	4 (36.6)	NS
Baseline RVD (mm)	3.04 ± 0.36	2.71 ± 0.31	<0.05
Postprocedure RVD (mm)	3.28 ± 0.24	2.89 ± 0.29	<0.05
Ostial location, n (%)	11 (84.6)	2 (18.1)	<0.05
Calcified lesions, n (%)	3 (23)	5 (45.4)	NS
Number of guiding catheters/patient	1.07 ± 0.2	1.7 ± 0.9	<0.05
Number of guide wires/patient	2.15 ± 1.34	2.17 ± 1.1	NS
Number of balloons/patient	1.53 ± 0.87	1.63 ± 0.8	NS
TL number of placed stents/patient	3.3 ± 1.54	2.27 ± 0.46	<0.05
TL average diameter stent (mm)	3 ± 0.3	2.62 ± 0.24	<0.05
TL average length stent (mm)	22.9 ± 6.5	21.5 ± 4.4	NS
Total number of treated lesions	1.76 ± 0.92	1.72 ± 0.78	NS
Total number of placed stents/patient	4 ± 1.65	3 ± 1.54	<0.05
Total average diameter stent (mm)	2.97 ± 0.35	2.6 ± 0.1	<0.05
Total average length stent (mm)	22.4 ± 4.94	21.4 ± 3.7	NS
Use of distal protection, n (%)	5 (38.4)	0 (0)	NS
Procedural time (min)	148 ± 39	135 ± 36	NS
Contrast amount (ml)	360 ± 112	399 ± 133	NS
Periprocedural abciximab, n (%)	8 (61.5)	5 (45.4)	NS

RVD, reference vessel diameter; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; TL, target lesion; SVG, saphenous vein graft.

TABLE III. Procedural and In-Hospital Outcomes

	SVG group ($N = 11$)	Native group ($N = 13$)	P value
Procedural success rate (%)	100	100	NS
Final TIMI flow grade 3, n (%)	11 (100)	13 (100)	NS
Hemodynamic instability, n (%)	2 (15.3)	0 (0)	NS
IABP, n (%)	1 (7.6)	0 (0)	NS
Temporary pacing, n (%)	1 (7.6)	0 (0)	NS
Perforation, n (%)	0 (0)	0 (0)	NS
In-hospital death, n (%)	0 (0)	0 (0)	NS
Postprocedural MI, n (%)	0 (0)	0 (0)	NS
Urgent TVR, n (%)	0 (0)	0 (0)	NS
Postprocedural CK levels (UI)	123 ± 66	99 ± 50	NS

IABP, intra aortic balloon pump; TVR, target vessel revascularization; TIMI, thrombolysis in myocardial infarction; SVG, saphenous vein graft; MI, myocardial infarction; CK, creatine-kinase.

RESULTS

Baseline and Procedural Variables

Baseline clinical and angiographic characteristics are shown in Tables I and II.

In our population, the median time from bypass surgery to the index percutaneous was 10 years (range: 10 months to 20 years). In the SVG group, distal embolic protection was used in 38.4%. There were no significant differences in the two groups except that patients with PCI for SVG versus native artery occlusion presented more often with acute coronary syndrome (46.1% vs. 9.0%; $P < 0.05$), three vessel disease (100% vs. 63.6%; $P < 0.05$), received a slightly higher number of stents (4 ± 1.65 vs. 3 ± 1.54; $P < 0.05$) and with a larger mean diameter (2.97 ± 0.35 vs. 2.6 ± 0.1 mm; $P < 0.05$).

Procedural and In-Hospital Outcomes

Procedural and In-Hospital Outcomes are summarized in Table III.

Both technical and procedural success rates were 100%. No death, postprocedural infarction, or urgent re-PCI occurred in either group. Two patients experienced hemodynamic instability, both in the SVG group. One patient needed an intra-aortic balloon pump (none in native vessel group) and one patient needed temporary pacing (none in native vessel group).

Follow-up Clinical Outcomes

Three-year follow up clinical outcomes are shown in Table IV.

One patient dropped out after 9.2 months (276 days). One patient in the native vessel group died 11 months (335 days) after the procedure; one patient in the SVG group died 24 months (720 days) after the procedure. There was one TVR in the native vessel group (13 months after the index procedure) and one in the SVG group (5.2 months after the index procedure). No MI or re-CABG occurred in the follow-up period. The cumulative MACE free survival rate at 36 months was 81.8% in native vessel versus 83.9% in the SVG group.

DISCUSSION

The main findings of this study are that SVG reopening instead of the native vessel is a feasible and an interesting option in selected cases and that DES use in this population is safe with good long-term outcomes. Undoubtedly this can be considered one of the most challenging and highest risk populations ever treated in the DES era: patients with previous CABG, treated with a PCI in SVGs or native vessels for a CTO. What today can be considered "real world clinical practice," albeit still not so common, was discouraged a few years ago; in an editorial published by our group in 1993 [1] it was suggested to avoid percutaneous treatment of SVG lesions and to opt for revascularization of the native vessel if re-CABG, as a serious alternative, was not feasible.

TABLE IV. Three-Year Follow-up Clinical Outcomes

	SVG group ($N = 11$)	Native group ($N = 13$)	P value
Deaths, n (%)	1 (7.6)	1 (9)	NS
MI, n (%)	0 (0)	0 (0)	NS
Re-CABG, n (%)	0 (0)	0 (0)	NS
Re-PCI, n (%)	1 (7.6)	1 (9)	NS
MACEs, n (%)	2 (15.3)	2 (18.1)	NS

MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; MACE, major adverse cardiac events; SVG, saphenous vein graft.

The 2005 ACC/AHA guidelines for PCI indicate that the average technical success rate of recanalizing CTO is 65%; advances in technical skills and introduction of new devices have enabled in some centers to reach a 70% or greater technical success rate, which anyway is still considerably lower compared with the 92% success rate of PCI for overall lesions [15–18].

Consistent with these data, technical success rate between July 2002 and October 2004 in our centre was 74.1%. It is well known that interventional maneuvers on vein grafts are difficult and often associated with a high risk of complications; lesion crossing, balloon inflation, and stent deployment can easily perforate the vein wall or dislodge friable atherosclerotic and thrombotic material, causing distal embolization and slow-flow or no-reflow phenomenon [1,19].

Which therefore were the elements that led the interventionist to attempt reopening a SVG instead of the native vessel?

The decision was basically taken on angiographic features: the presence of diffuse, complex, or ostial blunt lesions in tortuous, calcified native vessels deterred their recanalization while, on the other hand, good graft conditions, short shaft or ostial tapered SVG lesions or the presence of sequential grafts encouraged a reopening attempt.

DES, new protection devices, and antiplatelet drugs make the attempt easier. Recent studies reported that DES implantation (both sirolimus and paclitaxel eluting stents) reduced in-stent restenosis and improved both short- and long-term revascularization rates after successful CTO recanalization in native vessels compared with bare metal stents [20–22]. Moreover, distal protection devices (e.g. FilterWire EX) and platelet glycoprotein IIb/IIIa inhibitors have been shown to be effective in elective PCI in SVGs by reducing distal embolization and slow-flow or no-reflow phenomena [23–25].

In this study, the use of DES for CTO recanalization, associated with the use of antiplatelet drugs led to excellent postprocedural and in-hospital outcomes. No death, MI, urgent TVR, or distal embolization occurred in either group. Additionally, only two patients with PCI for SVG occlusion had in-hospital hemodynamic instability (15.3%), one requiring an IABP and one requiring temporary pacing.

Three-year follow-up outcomes are good especially considering the high baseline risk profile of our population: prior CABG, advanced age, prior infarction, three-vessel and diffuse coronary disease, and diabetes mellitus were common characteristics of this population. However, despite the encouraging outcomes of DES use, up to 50% of late cardiac events in patients with SVG lesions are due to disease progressions at different sites rather than the initial target [26,27]; so a high MACE rate should be expected in this population.

At 3 years, two patients died (one in each group) and two underwent a re-PCI (one in each group). MACE-free survival rate at 36 months in the native vessel and SVG groups were 81.8% and 83.9% respectively, without statistical difference between the groups.

This compares favorably with existing data on DES use for native vessel CTO treatment, with reported overall MACE-free survival rate at 6 and 12 months of 90–91% and 87–84% respectively [20,28,29], although still few data are available on DES use for SVGs CTO treatment. A recent report by Ge et al. showed an overall MACE-free survival at 6 months of 88.5% in SVG lesions [30], in line with the results of DES use on native vessels. Though based on a very small, highly selected population with peculiar angiographic features and though should be interpreted with great caution, these results show encouraging follow-up results probably thanks to DES, new guide wires generation, and new specific devices introduction. In selected cases, SVG recanalization instead of the native vessel with DES can therefore be an interesting option with a high procedural success rate; moreover, DES implantation in both SVG and native CTO lesions is associated with an equal effect on MACE-free survival at 3-year follow-up.

REFERENCES

1. de Feyter PJ, van Suylen RJ, de Jaegere PP, et al. Balloon angioplasty for the treatment of lesions in saphenous vein bypass grafts. J Am Coll Cardiol 1993;21:1539–1549.
2. de Jaegere PP, van Domburg RT, DeFeyter PJ, Ruygrok PN, van der Giessen WJ, van der Brand MJ, Serruys PW. Long-term clinical outcome after stent implantation in saphenous vein grafts. J Am Coll Cardiol 1996;28:89–96.
3. Fishman DL, Savage MP, Bailey S, Wermer JA, Rake R, Goldberg S. Predictors of restenosis after saphenous vein graft interventions. Circulation 1996;94 (Suppl I):I-621.
4. Ellis SG, Brener SJ, DeLuca S, Tuzcu EM, Raymond RE, Whitlow PL, Topol EJ. Late myocardial ischemic events after saphenous vein graft intervention-importance of initially "non-significant" vein graft lesions. Am J Cardiol 1997;79:1460–1464.

Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.
Published on behalf of The Society for Cardiovascular Angiography and Interventions (SCAI).

5. Olivari Z, Rubatelli P, Piscione F, Ettori F, Fonatanelli A, Salemme L, Giachero C, Di Mario C, Gabrielli G, Spedicato L, Bedogni F; TOAST-GISE Investigators. Immediate results and one-year clinical outcome after percutaneous coronary interventions in chronic total occlusions: Data from a multicenter, prospective, observational study (TOAST-GISE). J Am Coll Cardiol 2003; 41:1672–1678.
6. Hoye A, van Domburg RT, Sonnenschein, Serruys PW. Percutaneous coronary intervention for chronic total occlusions: The Thoraxcenter experience 1992–2002. Eur Heart J 2005;26:2630–2636.
7. de Feyter PJ. Percutaneous treatment of saphenous vein bypass graft obstructions: A continuing obstinate problem. Circulation 2003;107:2284–2286.
8. Walts AE, Fishbein MC, Marloff JM. Thrombosed, ruptured atheromatous plaques in saphenous vein coronary artery bypass grafts: Ten year's experience. Am Heart J 1987;114:718–723.
9. Solymoss BC, Nadeau P, Millette D, Campeau L. Late thrombosis of saphenous vein coronary bypass grafts related to risk factors. Circulation 1988;78 (Suppl I):I-140–I-143.
10. Motwani JG, Topol EJ. Aortocoronary saphenous vein graft disease: Pathogenesis, predisposition, and prevention. Circulation 1998;97:916–931.
11. Lie JT, Lawrie GM, Morris GC. Aortocoronary bypass saphenous vein graft artherosclerosis: Anatomic study of 99 vein grafts from normal and hyperlipoproteinemic patients up to 75 months postoperatively. Am J Cardiol 1977;40:906–914.
12. Kalan JM, Roberts WC. Morphologic findings in saphenous vein used as coronary arterial bypass conduits for longer than 1 year: Necropsy analysis of 53 patients, 123 saphenous veins, and 1865 five-millimeter segments of veins. Am Heart J 1990;119:1164–1184.
13. Pedersen SS, Denollet J, Ong AT, Serruys PW, Erdman RA, van Domburg RT. Impaired health status in Type D patients following PCI in the drug-eluting stent era. Int J Cardiol 2007; 114:358–365.
14. Rumsfeld JS, Magid DJ, Plomondon ME, Sacks J, Henderson W, Hlatky M, Sethi G, Morrison DA; Department of Veterans Affairs Angina With Extremely Serious Operative Mortality (AWESOME) Investigators. Health-related quality of life after percutaneous coronary intervention versus coronary bypass surgery in high-risk patients with medically refractory ischemia. J Am Coll Cardiol 2003;41:1732–1738.
15. Noguchi T, Miyazaki S, Morii I, Daikoku S, Goto Y, Nonogi H. Percutaneous transluminal coronary angioplasty of chronic total occlusions. Determinants of primary success and long-term clinical outcome. Catheter Cardiovasc Interv 2000;49:258–264.
16. Suero JA, Marso SP, Jones PG, Laster SB, Huber KC, Giorgi LV, Johnson WL, Rutherford BD. Procedural outcomes and long-term survival among patients undergoing percutaneous coronary intervention of a chronic total occlusion in native coronary arteries: A 20-year experience. J Am Coll Cardiol 2001;38: 409–414.
17. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention—Summary article: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI writing committee to update the 2001 guidelines for percutaneous coronary intervention). Circulation 2006;113:156–175.
18. Rubartelli P, Verna E, Niccoli L, Giachero C, Zimarino M, Bernardi G, Vassanelli C, Campolo L, Martuscelli E; Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche Investigators. Coronary stent implantation is superior to balloon angioplasty for chronic coronary occlusions. Six-year clinical follow-up of the GISSOC trial. J Am Coll Cardiol 2003;41:1488–1492.
19. Hong MK, Mehran R, Dangas G, Mintz GS, Lansky AJ, Pichard AD, Kent KM, Satler LF, Stone GW, Leon MB. Creatine kinase-MB enzyme elevation following saphenous vein graft intervention is associated with late mortality. Circulation 1999;100: 2400–2405.
20. Werner GS, Krack A, Schwarz G, Prochnau D, Betge S, Figulla HR. Prevention of lesion recurrence in chronic total coronary occlusions by paclitaxel-eluting stents. J Am Coll Cardiol 2004; 44:2301–2306.
21. Ge L, Lakovou L, Cosgrave J, Chieffo A, Montorfano M, Michev I, Airoldi F, Carlino M, Melzi G, Sangiorgi GM, Corvaja N, Colombo A. Immediate and mid-term outcomes of sirolimus-eluting stent implantation for chronic total occlusions. Eur Heart J 2005;26:1056–1062.
22. Hoye A, Tanabe K, Lemos PA, Aoki J, Saia F, Arampatzis C, Degertekin M, Hofma SH, Sianos G, McFadden E, van der Giessen WJ, Smits PC, de Feyter PJ, van Domburg RT, Serruys PW. Significant reduction in restenosis after the use of sirolimus-eluting stents in the treatment of chronic total occlusions. J Am Coll Cardiol 2004;43:1954–1958.
23. Baim DS, Wahr D, George B, Leon MB, Greenberg J, Cutlip DE, Kaya U, Popma JJ, Ho KK, Kuntz RE, Saphenous Vein Graft Angioplasty Free of Emboli Randomized (SAFER) trial investigators. Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. Circulation 2002;105:1285–1290.
24. Stone GW, Rogers C, Hermiller J, Feldman R, Hall P, Haber R, Masud A, Cambier P, Caputo RP, Turco M, Kovach R, Brodie B, Herrmann HC, Kuntz RE, Popma JJ, Ramee S, Cox DA, FilterWire EX Randomized Evaluation investigators. Randomized comparison of distal protection with filter-based catheter and a balloon occlusion and aspiration system during percutaneous intervention of diseased saphenous vein aorto-coronary bypass grafts. Circulation 2003;108:548–553.
25. Mathew V, Grill DE, Scott CG, Grantham JA, Ting HH, Garratt KN, Holmes DR Jr. The influence of abciximab use on clinical outcome after aortocoronary vein graft interventions. J Am Coll Cardiol 1999;34:1163–1169.
26. Keeley EC, Velez CA, O'Neill WW, Safian RD. Long-term clinical outcome and predictors of major adverse cardiac events after percutaneous interventions on saphenous vein grafts. J Am Coll Cardiol 2001;38:659–665.
27. Savage MP, Douglas JS Jr, Fischman DL, Pepine CJ, King SB III, Werner JA, Bailey SR, Overlie PA, Fenton SH, Brinker JA, Leon MB, Goldberg S. Stent placement compared with balloon angioplasty for obstructed coronary bypass grafts. Saphenous Vein De Novo Trial Investigators. N Engl J Med 1997;337:740–747.
28. Migliorini A, Moschi G, Vergara R, Parodi G, Carrabba N, Antoniucci D. Drug-eluting stent-supported percutaneous coronary intervention for chronic total coronary occlusion. Catheter Cardiovasc Interv 2006;67:344–348.
29. Hoye A, Lemos PA, Arampatzis CA, Saia F, Tanabe K, Degertekin M, Hofma S, McFadden E, Sianos G, Smits PC, van der Giessen WJ, de Feyter P, van Domburg RT, Serruys PW. Effectiveness of the sirolimus-eluting stent in the treatment of saphenous vein graft disease. J Invasive Cardiol 2004;16:230–233.
30. Ge L, Iakovou I, Sangiorgi GM, Chieffo A, Melzi G, Cosgrave J, Montorfano M, Michev I, Airoldi F, Carlino M, Corvaja N, Colombo A. Treatment of saphenous vein graft lesions with drug-eluting stents immediate and midterm outcome. J Am Coll Cardiol 2005;45:989–994.

CHAPTER 11

RETROGRADE SEPTAL APPROACH FOR A CHALLENGING CHRONIC TOTAL OCCLUSION OF THE RIGHT CORONARY ARTERY

Retrograde septal approach for a challenging chronic total occlusion of the right coronary artery

Imad Sheiban, Claudio Moretti, Giuseppe G.L. Biondi-Zoccai, Filippo Sciuto, Pierluigi Omedè, Primiano Lombardi, Emanuele Meliga, Marco Reviglione, Gian Paolo Ballari, Mario Bollati, Alfonso Gambino and Giampaolo Trevi

Journal of Cardiovascular Medicine 2007, 8:000–000

Division of Cardiology, University of Turin, Turin, Italy

Correspondence to Prof Imad Sheiban, Interventional Cardiology, Division of Cardiology, University of Turin, San Giovanni Battista-Molinette Hospital, Corso Bramante 88–90, 10126 Turin, Italy
Tel: +39 011 6336026; fax: +39 011 6967053; e-mail: isheiban@yahoo.com

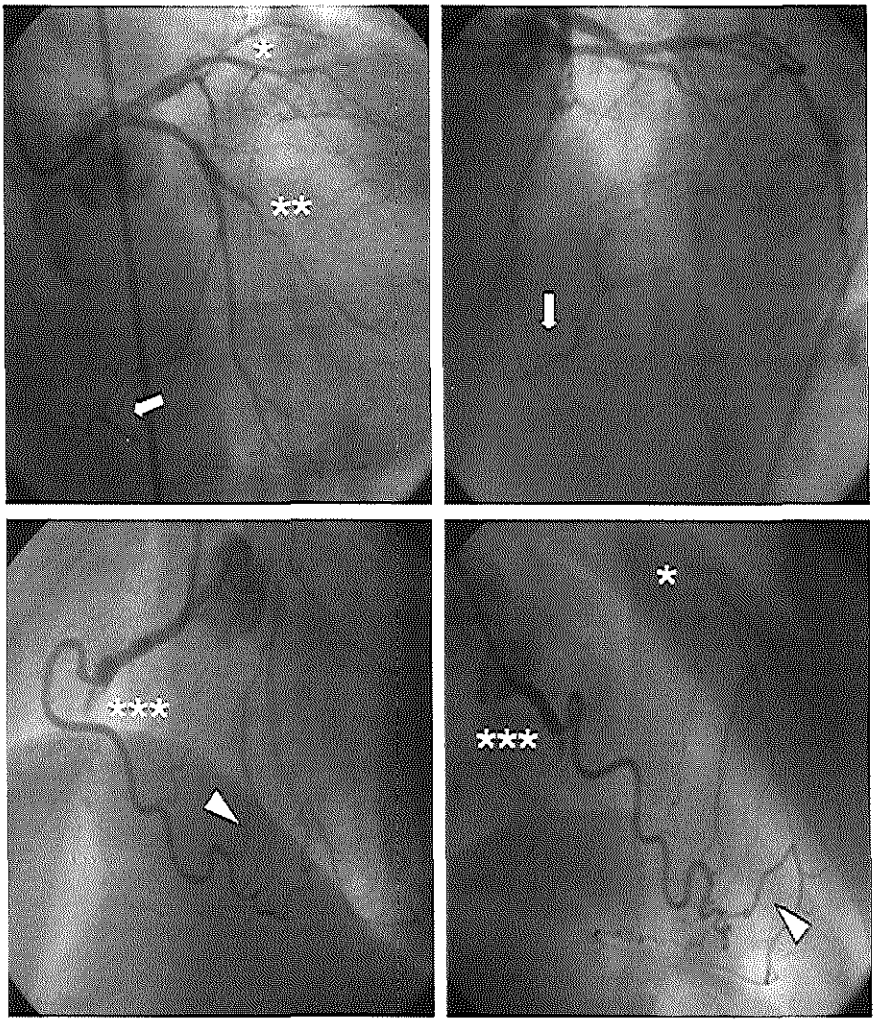
Received 15 February 2007 Revised 27 March 2007
Accepted 29 March 2007

A sizable portion of clinically relevant coronary obstructive lesions is constituted by chronic total occlusions (CTOs), and successful revascularisation of CTOs is thus pivotal for patients' prognosis and symptomatic relief. Unfortunately, the percutaneous approach to CTO is still fraught by a non-negligible risk of failure (ranging from 10% to 30%) [1]. Technical and technological developments have brought major improvements also in this field of interventional cardiology, and the percutaneous retrograde approach appears among the most promising and interesting techniques [2]. Only limited data are, however, available on this strategy. We hereby present the case of a patient with multivessel coronary disease who underwent successful recanalisation of a challenging CTO of the right coronary artery (RCA) by means of a septal retrograde approach.

The patient, a 78-year-old man known for chronic atrial fibrillation and ischaemic cardiomyopathy due to a remote anterior myocardial infarction, had been admitted to our institution for recurrent episodes of acute pulmonary oedema. He had previously (1988) undergone coronary angiography and percutaneous transluminal coronary angioplasty (balloon-only) in the left circumflex artery. Baseline electrocardiogram showed tachycardic atrial fibrillation, QS complexes in the precordial leads, and diffuse ST-T changes, in the absence of signs of myocardial necrosis in the inferior leads. Non-viability of the anterior left ventricular wall and, conversely, viability of the inferior wall were established by imaging tests. Coronary angiography during the current admission disclosed a CTO of the mid left anterior descending coronary artery (LAD), a critical stenosis of the first obtuse marginal branch, and a CTO of the mid RCA, with extensive collateral vessels connecting the LAD and RCA systems (Fig. 1). After expeditious treatment of the obtuse marginal branch by coronary angioplasty and stenting with two bare-metal stents (Driver, Medtronic, Milan, Italy) (Fig. 2a), we attempted to recanalise antegradely the RCA occlusion. Despite the use of both hydrophilic and non-hydrophilic stiff guidewires and the successful crossing of the occlusion, we could not gain lumen re-entry (Fig. 2b). We thus completely changed strategy and purposefully attempted retrograde recanalisation of the RCA through a proximal septal branch of the LAD using a 0.014" Choice PT wire (Boston Scientific, Genoa, Italy). We managed to reach the distal stump of the CTO and, after delivering a low-profile over-the-wire balloon (Maverick, Boston Scientific) for increased support (Fig. 2c), we crossed the CTO and achieved intra-luminal re-entry in the proximal RCA and ascending aorta (Fig. 2d). After extensive predilation by means of the balloon advanced retrogradely, the procedure was then completed by antegrade re-wiring (Choice PT) (Fig. 2e), predilation, stenting with two sirolimus-eluting devices (3.5 × 13 mm and 3.5 × 33 mm Cypher stents, Cordis, Milan, Italy) in the proximal and mid RCA, and balloon-only angioplasty of the distal tract of the RCA and its postero-lateral branch (Fig. 2f). The final angiographic result appeared satisfactory, with the notably persistence of brisk collateral flow from the acute marginal branch of the RCA to the LAD (Fig. 3).

The post-procedural course was uneventful, except for a minor and transient rise in serum creatinine, and the patient could be safely discharged a few days later on a 6-month prescription for clopidogrel, as well as long-term aspirin and warfarin (due to chronic atrial fibrillation, targeted at an international normalised ratio of 2.0–2.5). At 6-month clinical follow-up, the patient was still asymptomatic for angina, with minor dyspnoea during intense exertion (New York Heart Association class I), in the absence of other episodes of pulmonary oedema.

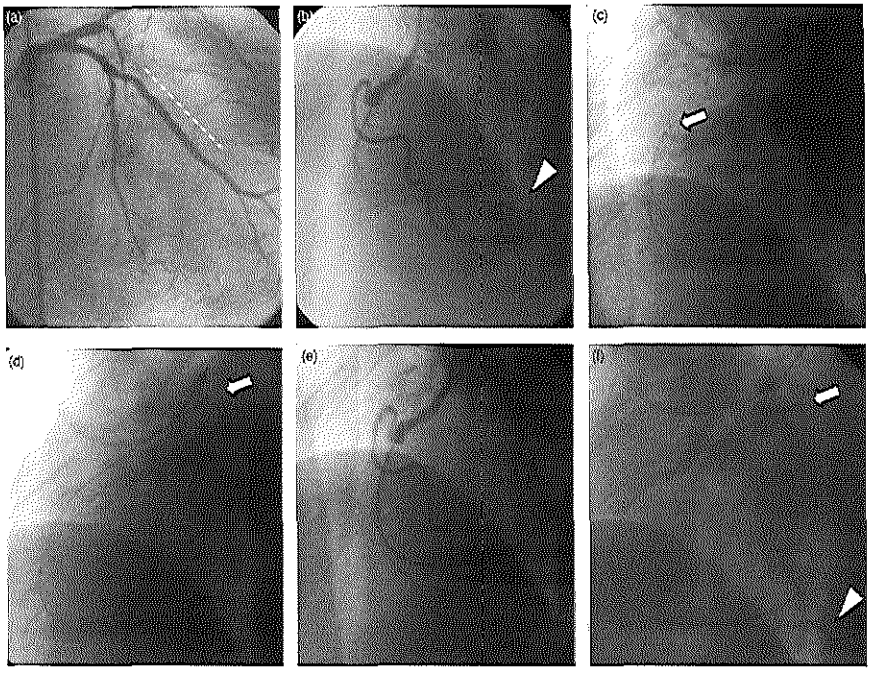
This clinical vignette, showing the feasibility and technical details pertinent to retrograde recanalisation of a coronary CTO, shows that this novel approach appears as a promising adjunct to the armamentarium of interventionalists. Coronary CTOs represent a sizable portion of



Baseline coronary angiography showing a chronic total occlusion of the mid left anterior descending coronary artery (*), a subocclusive stenosis of the first obtuse marginal branch (**) of the left circumflex artery, and a chronic total occlusion of the right coronary artery (***). Note the extensive collateral vessels from the left circumflex and left anterior descending coronary arteries to the distal right coronary artery (arrows), and from the acute marginal branch of the right coronary artery to the left anterior descending coronary artery (arrowheads).

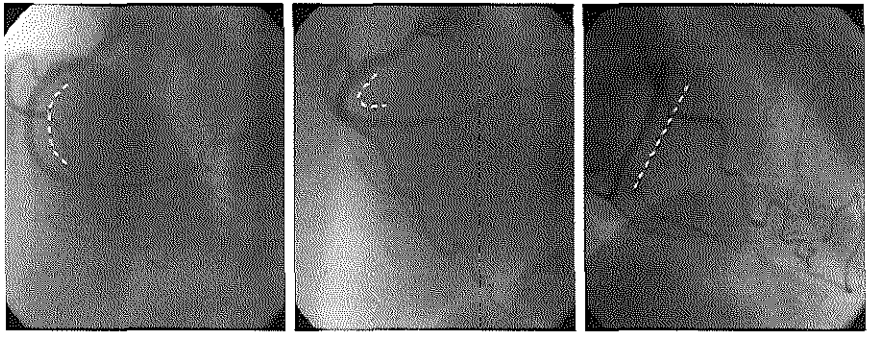
clinically significant coronary lesions, yet percutaneous approaches still face a non-negligible risk of failure in this lesion subtype [1]. Given the potential benefits associated with recanalisation of CTOs associated with symptoms or signs of myocardial ischaemia [3], such as the present one, it is pivotal to further develop devices and techniques in order to increase success rates. Among the most recent innovations, and on top of drug-eluting stents [4], is the retrograde approach, based on the recanalisation of a CTO by a retrograde fashion through the contralateral coronary artery and its collateral supply [2,5–9]. Despite its potential for increasing success rates and its diffusion also among peripheral interventionalists [8], only a handful of reports focusing on this technique are available, the largest to date including as few as 21 patients [8]. We believe that the present case provides further support for its very selected use in challenging CTOs.

Fig. 2



(a) Percutaneous transluminal coronary angioplasty and bare-metal stenting of the obtuse marginal branch (stents are highlighted by the dashed line). Percutaneous recanalisation of the right coronary artery occlusion, with initially unsuccessful antegrade approach (b), followed by successful retrograde wiring (c–e), pre-dilation with an over-the-wire balloon advanced retrogradely in a septal branch, and, finally, successful antegrade crossing of the occlusion (f). Arrows indicate the retrogradely advanced guidewire, and arrowheads the antegradely advanced wires.

Fig. 3



Final angiographic result after drug-eluting stenting of the proximal and mid right coronary artery and balloon-only dilation of the distal right coronary artery and its postero-lateral branch (stents are highlighted by the dashed lines). Notably, collateral vessels to the left anterior descending coronary artery were not injured by the revascularisation procedure.

On the other hand, this retrograde approach should be mainly considered as a last option, given that severe complications (including collateral vessel occlusion with septum haematoma and associated infarction) have already been reported [10]. Such recommendation for a very selective adoption of this strategy is even more relevant for operators without extensive experience in CTO recanalisation and unfamiliar with emergency pericardiocentesis. Nonetheless, the retrograde technique does not appear at preliminary analysis of the literature significantly more hazardous than other strategies for challenging CTOs (e.g., subintimal tracking and arterial re-entry) [8,11].

In conclusion, further and larger clinical investigations of this novel approach should be pursued to fully characterise its potential and limitations in the setting of the percutaneous management of carefully selected patients with challenging and clinically significant CTOs.

References

1 Rubartelli P, Verna E, Niccoli L, Giachero C, Zimarino M, Bernardi G, *et al.*, for the Gruppo Italiano di Studio sulle Stent nelle Occlusioni Coronariche Investigators. Coronary stent implantation is superior to balloon angioplasty for chronic coronary occlusions: six-year clinical follow-up of the GISSOC trial. *J Am Coll Cardiol* 2003; **41**:1488–1492.

2 Rosenmann D, Meerkin D, Almagor Y. Retrograde dilatation of chronic total occlusions via collateral vessel in three patients. *Catheter Cardiovasc Interv* 2006; **67**:250–253.

3 Abbate A, Biondi-Zoccai GG, Baldi A, Trani C, Biasucci LM, Vetrovec GW. The 'open-artery hypothesis': new clinical and pathophysiologic insights. *Cardiology* 2003; **100**:196–206.

4 Meliga E, Garcia-Garcia H, Kukreja N, Daemen J, Tanimoto S, Ramcharitar S, *et al.* Chronic total occlusion treatment in post-CABG patients: saphenous vein graft versus native vessel recanalization. Long-term follow-up in the drug-eluting stent era. *Catheter Cardiovasc Interv* (in press).

5 Surmely JF, Tsuchikane E, Katoh O, Nishida Y, Nakayama M, Nakamura S, *et al.* New concept for CTO recanalization using controlled antegrade and retrograde subintimal tracking: the CART technique. *J Invasive Cardiol* 2006; **18**:334–338.

6 Ozawa N. A new understanding of chronic total occlusion from a novel PCI technique that involves a retrograde approach to the right coronary artery via a septal branch and passing of the guidewire to a guiding catheter on the other side of the lesion. *Catheter Cardiovasc Interv* 2006; **68**:907–913.

7 Lane RE, Ilsley CD, Wallis W, Dalby MC. Percutaneous coronary intervention of a circumflex chronic total occlusion using an epicardial collateral retrograde approach. *Catheter Cardiovasc Interv* (in press).

8 Surmely JF, Katoh O, Tsuchikane E, Nasu K, Suzuki T. Coronary septal collaterals as an access for the retrograde approach in the percutaneous treatment of coronary chronic total occlusions. *Catheter Cardiovasc Interv* (in press).

9 Fusaro M, Dalla Paola L, Biondi-Zoccai G. Pedal-plantar loop technique for a challenging below-the-knee chronic total occlusion: a novel approach to percutaneous revascularization in critical lower limb ischemia. *J Invasive Cardiol* 2007; **19**:E34–E37.

10 Lin TH, Wu DK, Su HM, Chu CS, Voon WC, Lai WT, *et al.* Septum hematoma: a complication of retrograde wiring in chronic total occlusion. *Int J Cardiol* 2006; **113**:e64–e66.

11 Colombo A, Mikhail GW, Michev I, Iakovou I, Airoldi F, Chieffo A, *et al.* Treating chronic total occlusions using subintimal tracking and reentry: the STAR technique. *Catheter Cardiovasc Interv* 2005; **64**:407–411.

CHAPTER 12

COMPUTED TOMOGRAPHY IN TOTAL CHRONIC OCCLUSIONS (CTTO REGISTRY): RADIATION EXPOSURE AND PREDICTORS OF SUCCESSFUL PERCUTANEOUS INTERVENTION

Clinical research

EuroIntervention

Computed Tomography in Total coronary Occlusions (CTTO Registry): radiation exposure and predictors of successful percutaneous intervention

Héctor M. García-García[1], MD, MSc; Carlos A.G. van Mieghem[1], MD; Nieves Gonzalo[1], MD; Willem B. Meijboom[1], MD; Annick C. Weustink[1], MD; Yoshinobu Onuma[1], MD; Nico R. Mollet[1], MD, PhD; Carl Johann Schultz[1], MD; Emanuele Meliga[1], MD; Martin van der Ent[1], MD, PhD; Giorgios Sianos[1], MD, PhD; Dick Goedhart[2], PhD; Ad den Boer[1], PhD; Pim de Feyter[1], MD, PhD; Patrick W. Serruys[1]*, MD, PhD

1. Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands; 2. Cardialysis BV, Rotterdam, The Netherlands

Dick Goedhart is an employee of Cardialysis B.V. The remaining authors have no conflict of interest to declare.

KEYWORDS
Chronic total occlusion, computed tomography coronary angiography, radiation exposure

Abstract

Aims: There is no mention in the current "appropriateness criteria for CTCA" of the need of CTCA investigation prior to an attempt at recanalisation of a CTO. To define better the role of CTCA in the treatment of patients with CTOs, we performed CTCA in a consecutive cohort of eligible patients who were scheduled for percutaneous recanalisation of a CTO.

Methods and results: Symptomatic patients due to a CTO suitable for percutaneous treatment were included. One hundred and thirty-nine (142 CTOs) patients were studied. Overall success rate was 62.7%. By CTCA, the occlusion length was 24.9±18.3 vs. 30.7±20.7mm in successful and failed cases (p=0.1), but the frequency of patients with an occlusion length >15 mm was different, i.e. 63.2% vs. 82.7%, respectively (p=0.02). Severe calcification, (> 50% CSA) was more prevalent in failed cases (54.7% vs. 35.9%, p=0.03). Calcification at the entry of the occlusion was present in 58.5% of the failures vs. 41.6% of the successful cases (p=0.04), while calcium at the exit was not different. The length of calcification was 8.5±8.4 vs. 5.5±6.6 mm in the failed and successful cases respectively (p=0.027). By multivariable analysis, the only independent predictor of procedural success was the absence of severe calcification as defined by CTCA.

The mean effective radiation dose of the PCI was 39.3±30.1 mSv. The mean effective radiation dose of CT scan was 22.4 mSv: 19.2±6.5 mSv for contrast-enhanced scan, 3.2±1.7 mSv for calcium scoring scan.

Conclusions: More severe calcified patterns, as assessed by CTCA, are seen in failed cases. The radiation exposure during a CT scan prior to a CTO PCI is considerable, and further studies are required to determine whether this extra diagnostic study is warranted.

* *Corresponding author: Department of Cardiology, Erasmus Medical Center, Thoraxcenter, Ba583a, Erasmus MC, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands*
E-mail:p.w.j.c.serruys@erasmusmc.nl

Abbreviations list

CCA	Conventional coronary angiography
CTCA	Computed tomography coronary angiography
CTO	Chronic total occlusion
PCI	Percutaneous coronary intervention

Introduction

Since success rate have remained unchanged over the last few years, there has been a decrease in the number of attempted percutaneous coronary interventions (PCI) in patients with chronic total occlusions (CTO)[1]. In the search for new therapeutic approaches to reopen the occluded vessel, many new CTO-dedicated guidewires and devices have become available[2]. Until recently, innovative imaging tools to provide the operator guidance during the most exacting phase of the procedure, i.e. crossing the lesion, have been lacking. Commonly, in angiography these lesions appear as missing segments within two vessel ends. In addition, the angiogram does not provide reliable information with regard to the trajectory of the occluded segment, its length and tissue composition, variables that have been correlated with low procedural success rate[3]. Computed tomography coronary angiography (CTCA) has developed into a reliable noninvasive technique to evaluate a patient for the presence of obstructive coronary artery disease[4]. Although, preliminary data suggests that computed tomography coronary angiography (CTCA) might be of beneficial guidance in attempting revascularisation of a CTO[5], there is no mention in the current "appropriateness criteria for CTCA" of the need of a CTCA investigation prior to an attempt at recanalisation of CTO.

To define better the role of CTCA in the treatment of patients with CTOs, we performed CTCA in a consecutive cohort of eligible patients who were scheduled for percutaneous recanalisation of a CTO. We investigated angiographic and computed tomographic predictors of success and measured the amount of contrast material used during PCI and CTCA as well as the radiation exposure for both techniques.

Material and methods

Study population

Between April 2002 and March 2007, those eligible for this study included all consecutive patients presenting with symptomatic coronary artery disease due to a CTO. Specifically, patients without contra-indications for CTCA, suitable for percutaneous treatment who had provided written informed consent, were included. CTCA was considered contra-indicated in following situations: irregular heart rhythm, inability to sustain a sufficiently long breath hold (20 seconds with the 16-slice CT scanner, 15 seconds with the 64-slice or dual-source CT scanner), renal dysfunction (creatinine clearance <60 ml/min as defined with the Cockroft formula)[6], hearing disability, and known contrast allergy.

A CTO was defined as either an occlusion on angiography with no antegrade filling of the distal vessel other than via collaterals or minimal antegrade flow (TIMI flow 0 or 1)[7,8]. All included patients had a native vessel occlusion estimated to be at least of three months duration based on either a history of sudden chest pain, a previous acute myocardial infarction in the same target vessel territory, or the time between the diagnosis made on coronary angiography and PCI. The type of CTO was either *de novo* or due to in-stent restenosis.

The protocol was approved by the local ethics committee and is in accordance with the principles of Good Clinical Practice for Trials of Medicinal Products in the European Community and the Declaration of Helsinki. All patients signed a written informed consent.

All the CT scans were discussed between the operator of CTO procedure and someone trained to interpreting CTCA prior to the interventional procedure.

All interventional procedures were performed by operators who were highly experienced in the treatment of CTOs, with the interventional strategy left to the discretion of the operator. Wires were used in a stepwise progression, starting with a wire that had a relatively less traumatic tip (Graphix Intermediate, Boston Scientific Corporation, Miami, Fl, USA) or a hydrophilic wire (Choice PT Plus, Boston Scientific Corporation, or Crosswire NT, Terumo Corporation, Tokyo, Japan) and progressing to stiffer wires (Miracle, Asahi Intec, Nagoya, Japan) and specialised technologies (Safe-Cross, Intraluminal Therapeutics, Carlsbad, NM, USA; or The CROSSER™ CTO Recanalisation System FlowCardia Inc, CA, USA; or the Laser Guidewire, Spectranetics, Colorado Springs, CO, USA). Detailed description of these devices and explanation of our approach to treat CTO patients has been previously reported[2].

Procedural failure was defined as the inability to cross the occlusion with a guidewire.

All patients were pretreated with 300 mg of clopidogrel, which was continued at a dose of 75 mg/day for 6 months. All patients were advised to maintain aspirin (≥80 mg/day) lifelong.

Definitions

Procedural success: defined as successful opening of the chronic occlusion and restoration of flow (<50% residual stenosis and TIMI 2-3 flow).

Type of CTO: defined according to two characteristics, location (native vessel vs. graft) and quality (*de novo* or in-stent restenosis).

Occluded length: defined as the non-contrast enhanced segment of the vessel from the proximal to the distal end of the occlusion in the least foreshortened view on angiography or the 3-dimensional measurement of the occlusion using a dedicated software program (Circulation®, Siemens, Germany) of the CT workstation (Leonardo).

Stump morphology: defined as the entry site of the occlusion that has either a tapered- (central or eccentric) or a blunt appearance.

Side branch at the entry site: defined as the presence of any side branch, irrespective of the size, within 3 mm proximal to the entry of the occlusion.

Bridging collaterals: presence of multiple small collaterals connecting the proximal and distal lumens of the vessel by spanning through or around the occluded segment. This characteristic can only be measured by conventional angiography (CA).

Occlusion ends in bifurcation: the presence of a side branch larger than 1.5 mm within 3 mm distally to the distal end of the occlusion.
Rentrop classification[9]: grading of collateral filling was as follows: 0=none, 1=filling of side branches only, 2=partial filling of the epicardial segment, 3=complete filling of the epicardial segment. This classification only applies for conventional angiography since in CTCA the distal part of the vessel is almost always filled with contrast and thus can be regarded as Rentrop class 2 or 3.
Calcification: was defined as follows:

- By conventional angiography, defined as mild, moderate or severe.
- By CTCA, the number of separate calcium spots was counted and their length measured. The presence of calcium at the entry and exit side of the occlusion was annotated. All the spots were evaluated in a cross-sectional view to assess whether the calcification occupied more than 50% of the cross-sectional vessel area at any location within the occluded vessel segment. Finally, the amount of calcium in the occluded segment was quantified, using dedicated software.

Tortuosity: was defined as the presence of bends proximal to the lesion. By angiography, this feature was only scored in a binary fashion (yes/no), i.e. < or > than 45 degrees, while by CT, the angle of all the separate vessel bends was measured. (Figure 1)
Angulation: was defined as the presence of bends within the occluded segment. By angiography, only a binary scoring system was used (yes/no), while by CT, the angle was measured in subsequent bends within the occlusion. (Figure 2)

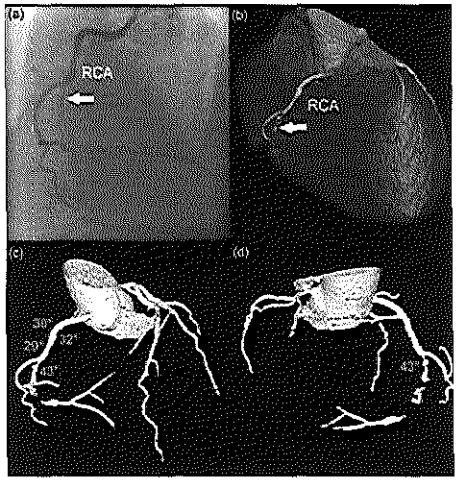


Figure 1. Assessment of tortuosity by computed tomography coronary angiography. (a) Angiographic image showing an occlusion (arrow) of the right coronary artery (RCA). (b) Volume-rendered CT image of the RCA, showing the occlusion (arrow) distal to the origin of the margo acutis. (c) 3-dimensional CT angiographic view of the coronary vasculature, illustrating the tortuosity of the vessel before the occlusion, with 4 consecutive bends. (d) same image as panel c but looking at the vessel from posterior; the final bend before the start of the occlusion is marked (43 degrees).

Conventional coronary angiography (CCA)

Two experienced observers who were unaware of the results of the CT scans analysed each film; consensus was needed for each assessed parameter. Quantitative angiographic analysis (CAAS II, Pie Medical, Maastricht, The Netherlands) was performed to measure the vessel diameter prior to the occlusion side. The length of the occluded vessel segment was also quantified. The other variables, i.e. location of the occlusion, morphology of the stump, the presence of a side branch in the vicinity of the entry (<3 mm), collaterals and calcification were reported qualitatively.

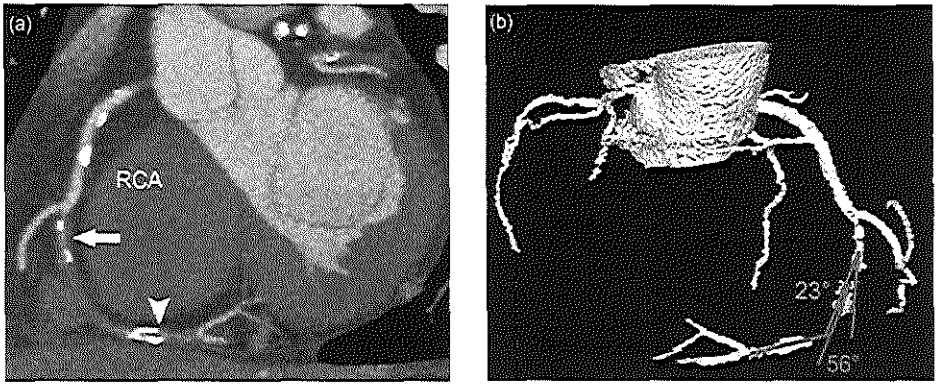


Figure 2. Assessment of angulation by computed tomography coronary angiography. (a) Maximal intensity projection of the right coronary artery (RCA) showing the vessel with the entry (arrow) and exit side (arrowhead) of the occlusion in one plane. (b) 3-dimensional CT angiographic view, illustrating the angulation within the occlusion; in this case 2 bends are visible.

Conventional coronary angiography: calculation of effective dose[10]

The Axiom study reports for each PCI procedure the used projections, the geometrical gantry settings and the generator settings for each digital cinematography (DCM), the used fluoroscopy time and the total dose-area product (DAP). The DAP is measured by an integral device in the x-ray tube, placed after the filters and the collimator and takes into account the quality, quantity, size and duration of the used x-ray beam.

A PC-based X-ray Monte Carlo program, from the Radiation and Nuclear Safety Agency, Helsinki, Finland, PCXMC, (reference Tapiovaara M, Lakkisto M, Servomaa A. A PC-Based Monte Carlo Program for calculating Patient Doses in Medical X-Ray Examinations. STUK-A139. Radiation and Nuclear Safety Agency, Helsinki, 1997) was used to estimate effective doses from conventional angiography. We did not correct for each gantry setting. We assumed all radiation was given in the Left Anterior Oblique 30 (LAO 30) projection, while the effective dose with careful simulation of all used gantry settings during DCM and fluoroscopy differed <2%. The focus-skin distance was 65 cm and the estimated entrance field size was 95 cm^2 with a quality of 70 kV.

CT patient selection, scan protocol and image reconstruction

A cardiac CT scan was performed in the fortnight before PCI. During the described study period 3 successive scan generations were used in our centre. Up to July 2004, CT data were acquired using a 16-slice CT scanner (Sensation 16, Siemens, Germany). From August 2004 to March 2006, CT data were acquired using a 64-slice CT scanner (Sensation 64, Siemens, Germany) and from April 2006 on the latest dual-source CT scanner (Somatom Definition, Siemens, Germany) was used. In the period until March 2006, we systematically slowed down the heart rate in patients with a heart rate above 65 bpm, using 100 mg metoprolol or a non-dihydropyridine calcium-antagonist (diltiazem 60-120 mg) orally 1 hour before the scan. An additional IV bolus of metoprolol (5-10 mg) was occasionally administered where the heart rate remained above 65 bpm. After that period we did not use extra medication to slow down the heart rate. Instead, nitrates were systematically given as a sublingual spray (0.4 mg) to all patients 5 minutes before initiation of the scan provided the systolic blood pressure was above 100 mmHg.

Scan parameters for each of the 3 scanner types were the following:

- 16-slice CT scanner: collimation 16×0.75 mm, tube rotation time 375 ms, tube voltage of 120 kV, table feed 3 mm per rotation. For the non-enhanced scan we used a tube current of 150 mAs and applied prospective x-ray tube modulation. For the angiographic scan we used a tube current that ranged between 500 and 600 mAs without the use of dose pulsing.
- 64-slice CT scanner: collimation 64×0.6 mm, tube rotation time 330 ms, tube voltage of 120 kV, table feed 3.8 mm per rotation. For the non-enhanced scan we used a tube current of 150 mAs and applied prospective x-ray tube modulation. For the angiographic scan we used a tube current that ranged between 850 and 960 mAs without the use of dose pulsing.
- dual-source CT scanner: collimation 64×0.6 mm, tube rotation time 330 ms, tube voltage of 120 kV. For the non-enhanced scan we used a tube current of 84 mAs per tube and full X-ray tube current was given during 50-70% of the RR interval. For the angiographic scan we used a tube current of 412 mAs per tube and limited this amount of tube current to 25-70% of the RR-interval. Pitch values were adapted to heart rate (minimal pitch value of 0.2 for slow heart rates, up to a maximal pitch value of 0.45 with higher heart rates).

The contrast-enhanced scan was obtained after the intravenous injection of 70-100 ml of contrast material (iomeprol, 400 mg iodine/ml, Iomeron® with the 16- and 64-slice CT scanner or iopromide, 370 mg iodine/ml, Ultravist® with the dual source CT scanner) through a large antecubital vein at a flow rate of 4-5 ml/sec, followed by 40ml of saline flush at 4 ml/s. A bolus tracking technique was used to monitor the appearance of contrast material in the ascending aorta. Once the signal in the ascending aorta reached a predetermined density level of 100 Hounsfield units, CT acquisition was automatically started during an inspiratory breath hold. Images were reconstructed using ECG-gating to obtain optimal, motion free image quality.

The scan data were reconstructed at various phases of the cardiac cycle using medium-to-smooth (B26f) and sharp (B46f) convolution kernel. Image reconstruction was retrospectively gated to the ECG. The position of the reconstructed window within the cardiac cycle was individually optimised to minimise motion artefacts. Datasets containing no or minimal motion artefacts were transferred to a remote workstation (Leonardo workstation, Siemens, Erlangen, Germany) for further evaluation.

CT coronary angiography: calculation of effective dose

The effective radiation dose was calculated from the scan parameters using dedicated software (ImPACT CT Patient Dosimetry Calculator, version 0.99x), as described in the European Guidelines on Quality Criteria for Computed Tomography (Available at: http://www.drs.dk/guidelines/ct/ quality/index.htm).

CT data analysis

Two experienced observers independently evaluated the CT data sets on both the original axial images and on multiplanar reformatted reconstructions for the presence of an occluded vessel. This initial assessment was performed blinded to the angiographic data. Subsequently, the observer was provided with the angiographic information, i.e. the occluded vessel in which PCI was performed, without having access to the angiographic images. After confirmation of the right vessel, the further CT analysis was performed without knowledge of the angiographic characteristics of the occluded vessel. In a few occasions, especially in case of heavy calcifications of the vessel, angiographic information on the start and end of the occlusion was provided to allow calculation of the occlusion length. To measure the length of the occlusion on CT we used a dedicated software program (Circulation®, Siemens, Germany), which allows creating a central lumen line through the

vessel. By rotating the vessel around this line the exact entry and exit point of the occlusion can be visualised, thus allowing us to measure the length of the occlusion along the 3-dimensional vessel path without foreshortening. (Figure 3).

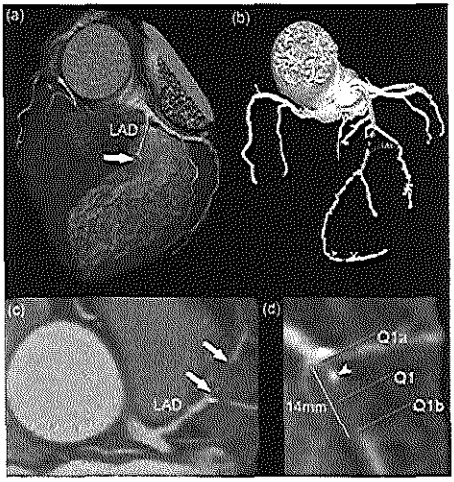


Figure 3. Measurement of the length of the occlusion by computed tomography coronary angiography. CT images showing an occlusion of the left anterior descending coronary artery (LAD). (a) Volume-rendered image showing the proximal part of the occlusion (arrow). (b) Using the Circulation® software the entire coronary tree can be extracted from the dataset. The start and end points for the vessel to be examined, in this example the LAD, are marked and a centreline through the middle of the vessel is displayed and labeled between these 2 points. (c) Maximal intensity projection showing the approximate length and composition, in this case non-calcified, of the occlusion. (d) After defining the centreline of the vessel, features of the occlusion such as length and composition can be evaluated. The markers Q1a and Q1b set the boundary marker at the beginning and end of the occlusion, which in this case measures 14mm. The proximal part of the occlusion shows a small amount of calcium (arrowhead).

Statistical analysis

Assumptions for normality were checked by Kolmogorov-Smirnov test and by visual assessment of Q-Q plots of residuals. Accordingly, log transformation was performed on the variables with skewed distribution. Continuous variables are presented as mean ±1SD and differences were compared using Student t test or Mann Whitney test. Categorical variables are presented as counts and percentages and differences were assessed by Fisher exact test or chi-square test, as appropriate. A two-sided p value of less than 0.05 indicated statistical significance.

The following variables were included in the multivariable analysis dataset: baseline characteristics (gender, age, diabetes mellitus, previous myocardial infarction, family history of coronary artery disease, smoking, hypertension, hypercholesterolaemia, previous PCI and previous coronary artery bypass surgery, vessel disease and target vessel), conventional angiographic characteristics (ostial location, stump morphology, presence of bridging collaterals, presence of side branch at the entry of the occlusion, degree of calcification and tortuosity [yes/no]); and CTCA characteristics (ostial location, stump morphology, presence of side branch at the entry of the occlusion, calcification -at entry, -at exit, >50% CSA, length of the calcification, angulation as a continuous variable, tortuosity as a continuous variable and length of the occlusion as a continuous variable. Due to collinearity problems, some variables were removed from the model. On the remainder of the variables we ran a backward selection procedure. Statistical analyses were performed with use of SAS V8.02.

Results

One hundred and thirty-nine (142 CTOs) consecutive patients were enrolled in this prospective registry of patients treated for a chronic total occlusion.

The mean age was 60.7±10.8 years, most of the patients being male (87.3%) (Table 1). For the majority of the patients (95.1%) this was the first attempt to open the CTO. Most of the occlusions were *de novo* lesions and the most frequently treated coronary artery was the left anterior descending (Table 2). Overall success rate was 62.7%.

CTO characteristics by conventional coronary angiography and CTCA

By conventional coronary angiography, the mean vessel diameter was larger in successful procedures (2.9±0.4 vs 2.1±0.7, p=0.02) as compared to procedural failures. Overall the length of the occlusion was 16.6±12.8 mm and there was no difference in successful vs. unsuccessful cases (16.0±12.7 and 18.0±13.4, p=0.5). The presence of a side branch at the entry was more frequently seen in failed cases (84.9 vs. 69.7%, p=0.03). Conversely, the presence of bridging collaterals was more frequently

Table 1. Baseline characteristics, n=139.

Age, yrs (mean+1SD)	60.7±10.8
Male (%)	87.3
Diabetes mellitus (%)	13.4
Hypertension (%)	40.1
Family history of CHD (%)	33.8
Current smoking (%)	23.9
Hypercholesterolaemia (%)	50.0
Previous ACS (%)	40.8
Previous PCI (%)	20.4
Previous CABG (%)	7.7
Vessel disease (%)	
One vessel disease	51.4
Two vessel disease	31.7
Three vessel disease	16.9
Attempts to reopen the CTO (%)	
First	95.1
Second	4.9

SD: standard deviation; CHD: cardiovascular heart disease; ACS: acute coronary syndrome; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft

Table 2. Morphologic CTO characteristics, n=142.

	Total	Failure, n=53	Success, n=89	p value
Conventional angiography characteristics				
Type of CTO (%)				
De novo	94.4	92.5	95.5	0.6
Target vessel (%)				0.5
Left anterior descending	42.3	50.9	37.1	
Left circumflex	13.4	11.3	15.7	
Right coronary artery	42.3	35.9	46.1	
Occluded length (mean±1SD)	16.6±12.8	18.0+13.4	16.0+12.7	0.5
Ostial location (Y/N) (%)	17.8	20.8	15.7	0.4
Stump morphology (%)				0.8
Central	28.2	28.3	28.1	
Eccentric	26.1	24.5	34.8	
Blunt	37.3	41.5	34.8	
Side branch at entry (Y/N) (%)	75.4	84.9	69.7	0.03
Bridging collaterals (Y/N) (%)	53.5	43.4	59.5	0.04
Collateral filling (Rentrop Classification [%])				0.45
0/1	21.5	22.7	13.5	
2	31.0	30.1	31.5	
3	42.3	37.7	44.9	
Angiographic calcification (%)				0.05
None/mild	40.1	39.6	40.4	
Moderate	32.4	22.6	38.5	
Severe	19.7	28.3	14.6	
Tortuosity (>45), (%)	45.8	43.4	47.2	0.58
Occlusion ends in bifurcation (Y/N)	23.2	17.0	27.0	0.18
Computed tomography angiographic characteristics				
Occluded length (mean±1SD)	27.1±19.4	30.7+20.7	24.9+18.3	0.1
Ostial location (Y/N) (%)	14.8	15.0	14.6	0.9
Stump morphology (%)				0.28
Central	16.4	17.0	15.7	
Eccentric	22.1	15.1	25.8	
Blunt	61.4	67.9	56.2	
Side branch at entry (Y/N)	42.3	43.4	41.6	0.8
Collateral filling (Rentrop Classification [%])				
0/1				
2				
3	100	100	100	1
Number of spots of calcium (%)				0.69
No	27.5	22.6	30.3	
One spot	43.0	46.2	40.4	
Two spot	19.0	18.9	19.1	
Three or more	10.5	11.3	10.1	
Calcium at the entry (%)	52.1	58.5	41.6	0.04
Calcium at the exit (%)	35.9	39.6	33.7	0.6
Calcium >50% CSA (Y/N) (%)	43.0	54.7	35.9	0.03
Calcium score of the occluded segment				
Volume (mm^3)	123.6±323.8	142.5±224.4	112.0±373.7	0.7
Equivalent mass (g)	25.0±81.0	24.5±33.4	25.4±100.1	0.9
Score (Agatston)	139.0±411.5	142.6±258.1	136.9±484.9	0.9
Tortuosity (%)				0.8
No	8.5	11.3	6.7	
One bend	43.3	41.5	43.8	
Two bends	31.2	26.4	33.7	
Three or more bends	12.8	15	11.2	
Angulation (%)				0.04
No	65.2	53.8	72.1	
One bend	29.7	40.4	23.3	
Two bends	1.4	0	2.3	
Three or more bends	3.6	5.7	2.3	

CTO, chronic total occlusion; CSA, cross-sectional area.

seen in successful cases (59.5 vs. 43.4%, p=0.04). Severe calcification, as defined qualitatively, was more prevalent in failed cases (28.3 vs. 14.6%, p=0.05). (Table 2)

By CTCA, the occlusion length was widely dispersed, mean 27.1±19.4 mm (range 2.6 to 93.4 mm) and longer as compared with CA. Although the occlusion length did not differ in successful as compared to failed cases (24.9±18.3 and 30.7±20.7, p=0.1), the frequency of patients with an occlusion length >15 mm was significantly different, i.e. 63.2% in those with procedural success vs. 82.7% in those with procedural failure (p=0.02).

CTOs without calcification were present in 27.5% of the treated lesions. The presence of severe calcification, defined as calcium that occupies more than 50% of the vessel cross-sectional area, was more prevalent in failures (54.7%) as compared to patients with a successful PCI procedure (35.9%) (p=0.03). The length of the calcified segments was longer in failed as compared to success cases (8.5±8.4 vs. 5.5±6.6 mm, p=0.027). When calcifications were present in the CTO, it was especially located at the entry side of the occlusion. Interestingly, calcification at the entry of the occlusion was present in 58.5% of the failures as compared to 41.6% of the successful cases (p=0.04), while the frequency of calcium at the exit was not different between the two patient groups. The absence of angulation in the occlusion was also a predictor of favourable outcome: procedural success was 72.1% in CTOs without angulation as compared to 53.8% in angulated CTOs (p=0.04) (Table 2).

Of note, the calcification patterns are affected by age but similar between genders (data not shown). Patients with severe calcification (>50% CSA) were older than their counterparts (63.9±9.0 vs. 58.3±11.4, p=0.002). Patients with longer calcification segments (cut-off set on >4.3mm – median of the length of calcified segments in this population) were also older (63.4±9.7 vs. 55.8±11.2, p=0.005). Patients with calcification at the entry of the occlusion segment were 61.4±10.2 vs. 55.4±10.6 year old, p=0.0007, and also patients with calcification at the exit were older 62.6±9.5 vs. 55.9±10.7 year old, p<0.0001.

In Table 3 a comparison between CCA and CTCA for the detection of calcium in the occlusion is shown. The angiographic estimation of the presence and severity of coronary calcification differed from the quantitative CT calcium score indices (i.e. volumetric score, equivalent mass or Agatston calcium score).

In the multivariable analysis the only variable that remained a significant predictor of procedural success, was the absence of severe calcification, i.e., calcium occupying >50% of the vessel CSA, as defined by CTCA (Table 4 and Figure 4).

Table 3. Comparison between CT calcium score and angiographic calcification score.

CTCA calcium scoring	Angiographic scoring	Mean±SD	Min	Max
Volume (mm^3)	None or mild	69.7±103.1	1.9	462
	Moderate	207.7±546.0	3.3	2712.5
	Severe	122.9±123.5	7.5	578
	p value	0.3		
Equivalent mass (g)	None or mild	12.6±16.6	0	60.16
	Moderate	39.5±138.1	0	726.95
	Severe	31.7±40.2	1.64	179.5
	p value	0.4		
Agatston score	None or mild	70.3±97.5	0.8	371.2
	Moderate	263.1±707.7	1.1	3515.8
	Severe	111.2±63.9	8.5	223.4
	p value	0.2		

CTCA: computed tomography coronary angiography; SD: standard deviation; Min: minimum; Max: maximum

Table 4. Angiographic and tomographic predictors of success: multivariate analysis.

	Coefficient	OR	95% CIs		p value
Previous PCI	−1.6	0.2	0.034	1.215	0.08
Side branch at the entry (Angio)	−1.9	0.15	0.02	1.184	0.07
Tortuosity (CTCA)	−0.01	0.99	0.969	1.002	0.09
Calcification >50% CSA (CTCA)	−1.8	0.17	0.036	0.747	0.02

PCI: percutaneous coronary intervention; CTCA: computed tomography coronary angiography; CSA: cross sectional area

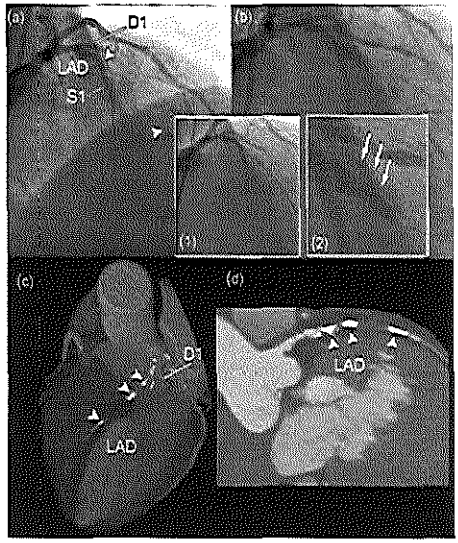


Figure 4. Assessment of calcification by computed tomography coronary angiography. Failed percutaneous coronary intervention in a patient with a chronic total occlusion of the left anterior descending coronary artery (LAD). (a) The angiographic borders of the occlusion are marked by arrows. (b) Final angiographic image showing persistent occlusion of the LAD. Insets show the wiring through the occlusion (inset 1) that appears to be in the false lumen as illustrated by the presence of contrast extravasation (arrows) once the wire is removed. (c) The volume-rendered CT image clearly shows heavy calcifications within the occluded segment (arrowheads). (d) Curved multiplanar reconstruction again highlighting the large calcifications (arrowheads) within the occlusion. D1, first diagonal branch. S1, septal branch.

Procedure related characteristics and effective radiation dose (Table 5)

Overall, the mean amount of contrast used was 455.4±202 ml and was not different between the patient treatment groups. The fluoroscopic time was higher in the failed cases as compared to the successful cases, 72.5 versus 53.1 minutes respectively, p=0.007. The mean effective radiation dose of the PCI procedure was 39.3±30.1 mSv. Overall, the mean effective radiation dose of the preprocedural CT scan was 22.4 mSv: 19.2±6.5 mSv for the contrast-enhanced scan, 3.2±1.7 mSv for the calcium scoring scan. The mean effective radiation dose per scanner type was: 14.4±5.7 mSv for 16-slice CTCA (n=34 patients), 20.1±1.6 mSv for 64-slice CTCA (n=42 patients) and 21.8±6.5 mSv for dual-source CTCA (n=63 patients).

Table 5. Procedure related characteristics and radiation parameters, n=142

	Total	Failure, n=53	Success, n=89	p value
Number of stents in the target vessel	1.8±1.4	0.7±0.9	2.9±1.3	<0.001
Average target vessel stent length (mm)	23.2±5.2	19.9±6.1	24.4±4.6	0.002
Average target vessel stent diameter (mm)	3.0±0.5	3.3±0.6	3.1±0.7	0.46
Biplane use (%)	70.8	76.6	68.8	0.4
Contrast used (ml)	455.4±201.9	457.8±214.7	454.2±195.8	0.93
Procedure time (min)	132.2±57.3	143.9±60.3	125.3±54.7	0.06
Fluoroscopic time (min)	60.3±40.1	72.5±41.9	53.1±37.5	0.007
Dose area product PCI (cGy*cm²)	16171.6±11539.0	17598±13765	15240±9814	0.3
Effective dose PCI (mSv)	39.26±30.1	42.5±36.5	37.1±25.1	0.34
Calcium scoring ctdi	10.5±5.1	10.1±5.8	10.7±4.8	0.6
Calcium scoring dlp	159.6±80.3	153.9±88.1	162.7±76.2	0.6
Effective dose calcium scoring (mSv)	3.2±1.7	3.1±1.8	3.3±1.6	0.5
CT ctdi	62.9±18.6	64.1±20.7	62.4±17.4	0.6
CT dlp	938.0±316.6	977.7±335.9	917.6±305.3	0.3
Effective dose CT (mSv)	19.2±6.5	20±7.1	18.8±6.2	0.3

CT: computed tomography; ctdi: computed tomography dose index; dlp: dose length index; mSv: millisievert

Discussion

In this registry of 139 patients we evaluated the possible role of CTCA when attempting PCI of CTOs. We found that the distribution rather than the amount of calcium impacts on the procedural outcome of this particular group of patients. Not unexpectedly, CTCA was more accurate than CCA for defining the morphological features of CTOs. In particular, we found that the assessment of calcification by CTCA was more predictive of success than CCA in the multivariate model. It is difficult to prove the added value of a preprocedural CT scan in terms of procedural outcome. However, it is fair to say that a better understanding of the anatomical features of an occluded vessel can modify our intentional treatment strategy[11]. Dedicated CTO wires and new treatment strategies have been developed recently and appear to be useful in selected cases[12]. However, these new tools need to be used judiciously, and in our view, in the right anatomical context. A promising new strategy to treat CTOs, is the retrograde approach which has been introduced as an alternative route for recanalisation of otherwise difficult or impossible lesions and is gaining acceptance among interventionalists due to its high success rate[13]. A possible explanation is the fact that calcium is more prevalent at the entry of the occlusion, so a higher chance to cross/break the distal cap and make progress retrograde would encourage the operator to continue until success is achieved (Figures 5a and 5b). Our data corroborate what intuitively was written in the consensus document from the EuroCTO club[14]: "the distal fibrous cap is often less resistant than the proximal cap". Another anatomical factor that favours the retrograde approach is the presence of side branch at the entry side of the occlusion that in our series was related to failed cases (Figures 5a and 5b).

The location of calcification is not only a strong determinant for crossing the lesion with the guidewire, but also influences the balloon selection. In severely calcified lesions small diameter balloons, i.e. 1.0, 1.1 and 1.25 mm, with a lubricious coating and acceptable shaft pushability are usually required[14].

Calcification of the coronary arteries has been related to age in several publications[15,16]. In our study, CTOs with longer and more severe calcified patterns were present in older patients. Also, the mean age of patients with calcifications at the entry and exit sides of the occlusion was significantly higher.

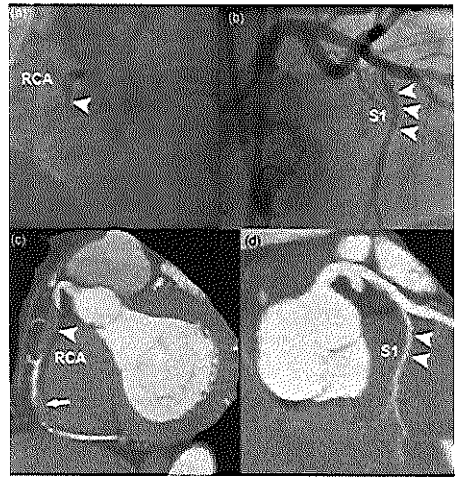


Figure 5a. Retrograde approach. (a) Angiographic image, showing proximal occlusion (arrowhead) of the right coronary artery (RCA). (b) Angiographic image of the left coronary artery, showing a large septal branch (arrowheads). (c) Corresponding CT image of the RCA showing 2 consecutive non-calcified occlusions of the vessel. (d) Corresponding CT image of the left coronary artery, also showing the large septal branch.

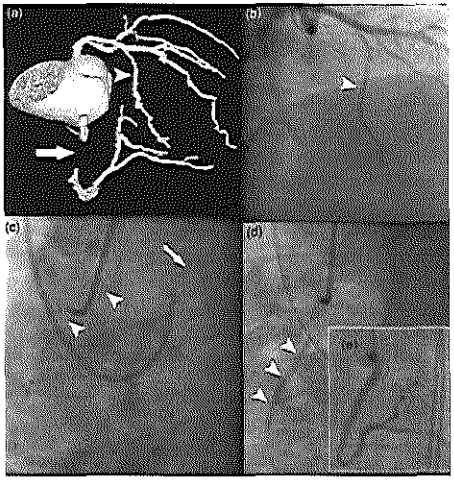


Figure 5b. Retrograde approach. Same patient as in 5a. Illustration of the percutaneous retrograde technique. (a) 3-dimensional CT angiographic view, showing he occlusion of the RCA (arrow) and the large septal branch (arrowhead). (b) Wiring of the septal branch (arrowhead). (c) The wire is introduced through the guiding catheter that is engaged in the left coronary artery (arrow) and was successfully advanced through the septal branch and finally retrograde through the RCA ending into the ascending aorta (arrowheads). (d) Balloon inflation over the wire that has been positioned retrograde in the RCA. (e) Final angiographic result after subsequent antegrade balloon dilatations and stenting of the vessel.

Undoubtedly, this is a high-risk subset of patients in different aspects and the decision to choose a percutaneous intervention should envisage maximal chances for success at minimal patient risk. The amount of contrast used and the radiation dose a patient receives are important variables that have an impact on patient safety. The contrast load during a CTO recanalisation attempt is higher as compared to non-CTO procedures[17,18]. In this study, the average amount of contrast used was 455.4 ml. In addition, a PCI of a CTO is often characterised by a long procedural time and a high radiation dose. Usually during the procedure one view is maintained, or two orthogonal views in case of biplane use, which leads to an intense exposition of the same skin areas[10] and body segments[14]. The average radiation dose of a PCI procedure in this study was 39.26 mSv. This is 8 times higher than the dose received during a conventional coronary angiogram[19]. In addition, patients received a mean radiation dose during the preprocedural cardiac CT scan of 22.4 mSv.

Clinical implications

In experienced centres, the success rate of a percutaneous CTO recanalisation attempt is on average 70%[8,14]. Knowing beforehand in which patients the chances of success are reasonably high appears to be worthwhile, as it has been shown that a failed recanalisation is associated with a worse outcome and a higher rate of major cardiac events[20]. The current study shows that CTCA is more precise than CCA for assessing the anatomical features of a CTO. At the cost of a significant additional amount of contrast and radiation, it would not be reasonable to propose a cardiac CT scan before each PCI attempt of a CTO. Instead, a cardiac CT scan seems most useful in patients in whom the angiographic features look unfavourable, or in patients in whom a second PCI attempt is contemplated. The decision whether or not to perform a contrast-enhanced scan after the calcium scoring scan depends on the information one wants to obtain: if the question is to have an idea of the amount of calcium in the occluded segment, a calcium scoring scan might be sufficient considering the fact that most of the radiation exposure derives from the contrast-enhanced scan. Pursuing a "complete scan", including the administration of contrast, might be preferred in case of a suspected long occlusion, where one aims to obtain information on the 3-dimensional course of the occlusion, including the distribution of calcium. In addition, the contrast and radiation exposure of the patient should become less of an issue in the near future: new scanning protocols are dramatically reducing the radiation dose of a contrast-enhanced scan to less than 3 mSv21 and scheduling the cardiac CT scan at least a few days before the PCI would not increase the risk of contrast nephropathy.

The radiation from a PCI is considerable, but necessary to do the procedure. Good arguments are needed before embarking on a percutaneous recanalisation attempt and this decision process in general should incorporate the symptomatic status of the patient, documentation of myocardial ischaemia and, if possible, data with regard to the pre-procedural chances of success. The latter argument would be in favour of performing a cardiac CT scan in selected cases: patients in whom the CT characteristics of a CTO are unfavourable for PCI might be considered for an alternative therapeutic modality, i.e. medical treatment or bypass surgery.

Limitations of the study

Despite the fact that we failed to provide accurate data for occlusion duration, which is an important marker of procedure failure[5], we performed a detailed and selective quantification of the calcium present in the occluded segment, for which occlusion duration is a surrogate marker as shown in a pathological study where fibrocalcific plaque increased with CTO age ($p=0.008$)[22].

Although all the CTCA scans were discussed between the operator and someone trained in interpreting CTCA prior to the interventional procedure, there was no formal documentation of the changes in approach for treating the CTO in light of the CTCA findings. Thus, it was difficult to measure to what extent this knowledge concerning the CTO characteristics by CTCA impacts on the success rate. In order words, a severely calcified and long lesion might have discouraged the operator from a longer attempt.

In case of severe calcifications of the vessel, we relied on angiographic data to determine the length of the occlusion by CTCA. Although a limitation in this study, the repercussion in clinical practice would be minor, as the angiographic data are an essential component of the therapeutic decision process for a given patient. As mentioned in the discussion above, we would only recommend a cardiac CT scan in selected cases to complement the angiographic information.

Conclusion

Evaluation of CTOs by means of CTCA offers a better description of its anatomical features as compared to conventional angiography and predicts procedural success in patients referred for PCI. More specifically, the presence of severe calcification, i.e. calcium occupying >50% of the vessel CSA, as determined by CTCA is an independent predictor of procedural failure. The radiation exposure and amount of contrast used during a PCI attempt is considerable. The judicious use of a preprocedural cardiac CT scan makes sense and might modify the approach in case PCI is attempted or could drive the physician's preference to an alternative therapeutic modality, i.e. medical treatment or bypass surgery.

References

1. Abbott JD, Klp KE, Vlachos HA, Sawhney N, Srinivas VS, Jacobs AK, Holmes DR, Williams DO. Recent trends in the percutaneous treatment of chronic total coronary occlusions. *Am J Cardiol* 2006;97:1691-6.

2. García-García HM KN, Daemen J, Tanimoto S, van Mieghem C, Gonzalo N, van der Ent M, Sianos G, de Feyter P, Serruys PW. Contemporary Treatment of Patients with Chronic Total Occlusion: Critical Appraisal of Different State-of-the-art Techniques and Devices. *EuroInterv* 2007;3;188-196.

3. Puma JA, Sketch MH Jr, Tcheng JE, Harrington RA, Phillips HR, Stack RS, Califf RM. Percutaneous revascularization of chronic coronary occlusions: an overview. *J Am Coll Cardiol* 1995;26:1-11.

4. Achenbach S. Computed tomography coronary angiography. *J Am Coll Cardiol* 2006;48:1919-28.

5. Mollet NR, Hoye A, Lemos PA, Cademartiri F, Sianos G, McFadden EP, Krestin GP, Serruys PW, de Feyter PJ. Value of preprocedure multislice computed tomographic coronary angiography to predict the outcome of percutaneous recanalization of chronic total occlusions. *Am J Cardiol* 2005;95:240-3.

6. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.

7. Hoye A, Tanabe K, Lemos PA, Aoki J, Saia F, Arampatzis C, Degertekin M, Hofma SH, Sianos G, McFadden E, van der Giessen WJ, Smits PC, de Feyter PJ, van Domburg RT, Serruys PW. Significant reduction in restenosis after the use of sirolimus-eluting stents in the treatment of chronic total occlusions. *J Am Coll Cardiol* 2004;43:1954-8.

8. Stone GW, Reifart NJ, Moussa I, Hoye A, Cox DA, Colombo A, Bairn DS, Teirstein PS, Strauss BH, Selmon M, Mintz GS, Katoh O, Mitsudo K, Suzuki T, Tamai H, Grube E, Cannon LA, Kandzari DE, Reisman M, Schwartz RS, Bailey S, Dangas G, Mehran R, Ablzaid A, Moses JW, Leon MB, Serruys PW. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. *Circulation* 2005;112:2364-72.

9. Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol* 1985;5:587-92.

10. den Boer A, de Feijter PJ, Serruys PW, Roelandt JR. Real-time quantification and display of skin radiation during coronary angiography and intervention. *Circulation* 2001;104:1779-84.

11. Van Mieghem CA, van der Ent M, de Feyter PJ. Percutaneous coronary intervention for chronic total occlusions: value of preprocedural multislice CT guidance. *Heart* 2007;93:1492.

12. Saito S, Tanaka S, Hiroe Y, Miyashita Y, Takahashi S, Satake S, Tanaka K. Angioplasty for chronic total occlusion by using tapered-tip guidewires. *Catheter Cardiovasc Interv* 2003;59:305-11.

13. Kukreja N, Serruys PW, Sianos G. Retrograde recanalization of chronically occluded coronary arteries: illustration and description of the technique. *Catheter Cardiovasc Interv* 2007;69:833-41.

14. Di Mario C WG, Sianos G, Galassi AR, Buttner J, Dudek D, Chevalier B, Lefevre T, Schofer J, Koolen J, Sievert H, Reimers B, Fajadet J, Colombo A, Gershlick A, Serruys PW, Reinfart N. European Perspective in the Recanalization of Chronic Total Occlusions (CTO): consensus document from the EuroCTO Club. *EuroInterv* 2007;3:30-43.

15. Kronmal RA, McClelland RL, Detrano R, Shea S, Lima JA, Cushman M, Bild DE, Burke GL. Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: results of 1,764 patients. *J Am Coll Cardiol* 2001;37:451-7.

16. Kronmal RA, McClelland RL, Detrano R, Shea S, Lima JA, Cushman M, Bild DE, Burke GL. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2007;115:2722-30.

17. Marenzi G, Assanelli E, Marana I, Lauri G, Campodonico J, Grazi M, De Metrio M, Galli S, Fabbiocchi F, Montorsi P, Veglia F, Bartorelli AL. N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. *N Engl J Med* 2006;354:2773-82.

18. Le Feuvre C, Batisse A, Collet JP, Batisse JP, Choussat R, Beygui F, Helft G, Montalescot G, Metzger JP.Cardiac events after low osmolar ionic or isosmolar nonionic contrast media utilization in the current era of coronary angioplasty. *Catheter Cardiovasc Interv* 2006;67:852-8.

19. Morin RL, Gerber TC, McCollough CH. Radiation dose in computed tomography of the heart. *Circulation* 2003;107:917-22.

20. Hoye A, van Domburg RT, Sonnenschein K, Serruys PW. Percutaneous coronary intervention for chronic total occlusions: the Thoraxcenter experience 1992-2002. *Eur Heart J* 2005;26(24):2630-6.

21. Husmann L, Valenta I, Gaemperli O, Adda O, Treyer V, Wyss CA, Veit-Haibach P, Tatsugami F, von Schulthess GK, Kaufmann PA. Feasibility of low-dose coronary CT angiography: first experience with prospective ECG-gating. *Eur Heart J* 2008;29:191-7.

22. Srivatsa SS, Edwards WD, Boos CM, Grill DE, Sangiorgi GM, Garratt KN, Schwartz RS, Holmes DR Jr. Histologic correlates of angiographic chronic total coronary artery occlusions: influence of occlusion duration on neovascular channel patterns and intimal plaque composition. *J Am Coll Cardiol* 1997;29:955-63.

PART 3

INTERVENTIONS IN HIGH RISK PATIENTS

CHAPTER 13

PACLITAXEL-ELUTING STENTS FOR THE TREATMENT OF COMPLEX CORONARY LESIONS: IMMEDIATE AND 12-MONTH RESULTS

Paclitaxel-eluting stents for the treatment of complex coronary lesions: immediate and 12-month results

Imad Sheiban, Gian Paolo Ballari, Claudio Moretti, Walter Grosso Marra, Emanuele Meliga, Pierluigi Omedè, Filippo Sciuto and Gian Paolo Trevi

Objective One of the drug-eluting stents that have been introduced into clinical practice is the paclitaxel-eluting stent (PES). Several randomised, controlled clinical trials have already been conducted to evaluate the safety and efficacy of this stent, but data regarding clinical practice are still lacking. The aim of this study was to evaluate the safety and efficacy of PESs in a 'real-world' population.

Methods Two hundred and seventy-three patients with a high cardiovascular risk profile and complex coronary lesions were treated with PESs. Each patient was categorised using the following parameters: cardiovascular risk factors, clinical history, clinical presentation, angiographic pattern, and procedural characteristics. Primary endpoints were major adverse cardiac events (cardiovascular death, coronary artery bypass grafting, myocardial infarction, stroke, target vessel revascularisation, target lesion revascularisation, and remote revascularisation).

Results A low rate of intraprocedural and periprocedural complications was observed. During the clinical follow-up period (mean 10.5 ± 4.2 months), 78% of patients were event-free. Twenty-six patients (9.8%) underwent target vessel revascularisation, but only 11 of them (4.2%) had target lesion revascularisation. Seven patients (2.7%) had myocardial infarction, and cardiac death occurred in two patients (0.76%). Only one case (0.37%) of subacute stent thrombosis and one case of late stent thrombosis were observed.

Conclusions The present study demonstrates that the use of PESs is safe and effective also in patients with a high cardiovascular risk profile and complex coronary lesions. *J Cardiovasc Med* 8:582–588 © 2007 Italian Federation of Cardiology.

Journal of Cardiovascular Medicine 2007, 8:582–588

Keywords: coronary angioplasty, coronary artery disease, coronary restenosis, drug-eluting stents, paclitaxel-eluting stents

Interventional Cardiology, Division of Cardiology, University of Turin, San Giovanni Battista Hospital, Turin, Italy

Correspondence to Prof. Imad Sheiban, Interventional Cardiology, Division of Cardiology, University of Turin, San Giovanni Battista Hospital, Corso Bramante 88–90, 10126 Torino, Italy
Tel: +39 011 6336026; fax: +39 011 6967053; e-mail: isheiban@yahoo.com

Received 8 February 2006 Accepted 27 July 2006

Introduction

Coronary restenosis after successful percutaneous coronary intervention (PCI) has ever been the major problem limiting the efficacy of this technique [1]. Several strategies have been attempted to face restenosis [2–14], the latest of which was the use of drug-eluting stents [15–20]. One of these devices introduced into clinical practice is the paclitaxel-eluting stent (PES) (TAXUS Express2, Boston Scientific Corp., Natick, Massachusetts, USA) [21–25]. At present, several randomised, controlled clinical trials have been conducted to evaluate the safety and efficacy of this stent, albeit complex patients with complex lesions were often excluded, enrolling preferably patients with single and de novo lesions. The TAXUS IV trial [26,27], for example, enrolled 1314 patients with single de novo lesions who were randomised to treatment with a slow-release PES versus a bare-metal stent. Also the TAXUS VI trial [28] (including 448 patients with complex, long coronary lesions randomised to treatment with a moderate-release PES versus a bare-metal stent) enrolled patients with de novo target lesions located within a single native coronary vessel with a reference vessel diameter between 2.5 and 3.5 mm. In both these trials, patients with previous drug-eluting stent implantation, recent or acute myocardial infarction (MI), low left ventricular ejection fraction, left main or ostial disease, bifurcation lesions or totally occluded vessels, which are all conditions frequently met by interventional cardiologists in clinical practice, were excluded.

The aim of the present study was to evaluate the safety and efficacy of PESs when implanted in 'real-world' patients, in a high cardiovascular risk population with complex coronary lesions.

Methods

Patient population and protocol

From May 2003 to December 2004, a total of 273 consecutive patients with a high cardiovascular risk profile and complex coronary lesions undergoing coronary angioplasty and PES implantation were included in the study.

Table 1 Baseline clinical characteristics of the study population ($n = 273$)

Cardiovascular risk factors	
Hypertension	79.5%
Diabetes	34.8%
Hyperlipidaemia	70%
Family history of CAD	17.9%
Active smoking	41.8%
History of CAD	59.3%
Previous MI	35.9%
Previous CABG	22%
Previous PCI	35.5%
Chronic renal failure	6%
Peripheral arteriopathy	17.2%

CABG, coronary artery bypass graft; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Patients with contraindications to double antiplatelet or anticoagulation therapy were excluded. Informed consent was obtained in accordance with the Declaration of Helsinki.

Baseline clinical and angiographic characteristics are shown in Tables 1, 2 and 3. The following baseline parameters were assessed in all patients: cardiovascular risk factors (age, sex, hypertension, diabetes, hyperlipidaemia, family history for coronary artery disease [CAD] and active cigarette smoking), presence of prior MI, previous coronary artery bypass graft (CABG) or PCI, presence of specific comorbidities such as chronic renal failure and peripheral vasculopathy, clinical presentation (ST-elevation MI [STEMI], non-ST-elevation MI [NSTEMI], unstable angina, stable angina, ventricular arrhythmias, acute pulmonary oedema or instrumental signs of ischaemia) and angiographic pattern (extension of CAD and lesion location).

Procedural characteristics included the following parameters: number of treated vessels (single or multivessel treatment), number of PESs per patient, treatment of bifurcation lesions with single or double stent, final kissing balloon, debulking procedures (directional or rotational atherectomy), and use of pressure wire or intravascular ultrasound-guided revascularisations.

Pre-procedural and post-procedural electrocardiograms were performed, and cardiac enzymes were measured at baseline, after the procedure, and daily until closure of the enzymatic curve.

Table 2 Indications for angiography and percutaneous coronary intervention

STEMI	9.5%
NSTEMI	21.6%
Unstable angina	42.5%
Stable angina	12.5%
Instrumental signs of ischaemia	13.9%

NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

Table 3 Angiographic and procedural data

Single-vessel disease	21.2%
Multivessel disease	78.8%
Type of treated lesion	
Total occlusion	19.4%
Ostial lesion	15%
Bifurcation lesion	18.7%
In-stent restenosis	10.7%
Left main disease	7.7%
Venous graft stenosis	3%
Adjunctive devices and medications	
Directional or rotational atherectomy	2.9%
Pressure wire evaluation	1.8%
IVUS evaluation	1.1%
Glycoprotein IIb/IIIa inhibitors	20.1%
Single-vessel treatment	43.2%
Multivessel treatment	56.8%

IVUS, intravascular ultrasound.

Study medications

Aspirin was administered to all patients before the procedure and indefinitely thereafter. A loading dose of 300 mg of clopidogrel was recommended before catheterisation followed by clopidogrel 75 mg/day or ticlopidine 250 mg twice daily for at least 6 months after the procedure. Glycoprotein IIb/IIIa inhibitor use was at the operator's discretion.

Follow-up

Clinical follow-up was scheduled for all patients after 1 month and then every 3 months until the end of the observational period (clinical follow-up ended for all patients on 30 April 2005). We reported results at 3, 6 and 12 months of follow-up (that we considered as mid-term results) and outcomes at the closure of the study. Angiographic control was performed only if non-invasive stress tests or clinical presentation (recurrence of angina) were suggestive of ischaemia.

Endpoints

Primary endpoints were major adverse cardiac events (MACEs), namely cardiovascular death, CABG, MI (either STEMI or NSTEMI), stroke, target vessel revascularisation (TVR), target lesion revascularisation (TLR), and remote revascularisation.

Statistical analysis

Continuous variables are expressed as mean ± SD, discrete variables are reported as percentages. Univariate analysis was conducted to evaluate the presence of correlations between single clinical, angiographic and procedural parameters and the recurrence of intrahospital adverse events or MACEs during the follow-up. Odds ratios (ORs), 95% confidence intervals (CIs) and P values were calculated for subgroup comparison. MACE-free survival distributions were assessed according to the Kaplan–Meier method.

Results

Patient and lesion characteristics

The baseline clinical and angiographic characteristics are summarised in Tables 1, 2 and 3. Essential hypertension was present in 79.5% of patients, diabetes in 34.8%, hyperlipidaemia in 70%, family history of CAD in 17.9%, and active smoking in 41.8% (Table 1). Previous MI was present in 35.9% of patients, 22% had a previous CABG, and 35.5% had a previous PCI.

Clinical indications for angiography and PCI were represented by unstable angina in 42.5% of patients, NSTEMI in 21.6%, stable angina in 12.5%, STEMI in 9.5%, and instrumental signs of ischaemia in 13.9% (Table 2). At angiographic evaluation (Table 3), 78.8% of patients had multivessel disease, 19.4% had total occlusion lesions, 15% ostial lesions, 18.7% bifurcation lesions, and 10.7% in-stent restenosis.

A total of 362 lesions were treated and 401 PESs were deployed (mean 1.47 ± 0.64 stents per patient, range 1–6), with a mean diameter of 3.1 ± 0.3 mm and a mean length of 17.04 ± 5.69 mm. Lesion distribution was the following: 7.7% in the left main coronary artery, 38.7% in the left anterior descending coronary artery, 20.4% in the left circumflex coronary artery (CX), 26.3% in the right coronary artery, 3.9% in the ramus, and 3% in the venous graft; 56.8% of patients underwent multivessel treatment. Directional or rotational atherectomy was used in 2.9% of patients; pressure wire and intravascular ultrasound were used in very few patients (pressure wire 1.8%, intravascular ultrasound 1.1%). A large proportion of lesions (76.3%) were type B2/C. During the procedure, glycoprotein IIb/IIIa inhibitors were administered to 20.1% of treated patients.

Double antiplatelet therapy with acetylsalicylic acid (administered to all patients before the procedure and indefinitely thereafter) and clopidogrel 75 mg/day or ticlopidine 250 mg twice daily was administered to all patients for at least 6 months after the procedure. In only two cases (0.76%), the clopidogrel or ticlopidine therapy was continued up to 12 months.

Table 4 Intraprocedural and periprocedural complications

Procedural success	100%
Procedural or in-hospital death[a]	0.4%
Post-procedural myocardial infarction[b]	4%
Acute or subacute in-stent thrombosis	0.4%
Stroke[a]	0.4%
Emergency coronary artery bypass graft	0%

[a] Referred to the same patient, deceased for a stroke 8 days after the procedure.
[b] Defined as an increase in cardiac enzymes of at least three times the basal values.

Intraprocedural and periprocedural complications

Table 4 shows intraprocedural and in-hospital adverse events. Procedural success (defined as residual stenosis <20% after stent deployment) was obtained in all patients. No cases of intraprocedural death occurred; in-hospital death occurred in one patient (0.4%), an 84-year-old female patient, with a history of CAD, previous MI and PCI, who underwent PCI for a NSTEMI. Two critical lesions in the middle segment of the left anterior descending coronary artery were successfully treated (the first one with a PES and the second one with a bare-metal stent), but the patient died from stroke 8 days after the procedure.

Post-procedural MI (defined as an increase in the cardiac enzyme creatine kinase-MB of at least three times the basal value) occurred in 11 patients (4%); no incidents of acute in-stent thrombosis or emergency CABG occurred; the subacute in-stent thrombosis rate was 0.4% (one patient) (Table 4). This event occurred in a 77-year-old female patient, with a high cardiovascular risk profile, who underwent PCI and multiple PES implantation for a NSTEMI (two PESs in the left anterior descending coronary artery and one PES in the CX). Four days after the procedure, she had angina associated with electrocardiographic modifications. An angiographic evaluation was performed and revealed in-stent thrombosis of the PES deployed in the CX (probably due to stent underexpansion), which was successfully treated with multiple dilatations with high-pressure balloons.

Follow-up events

Clinical follow-up results are shown in Table 5. Since the overall study patients were treated at different subsequent times (from May 2003 to December 2004) and

Table 5 Clinical events at follow-up

	3 months ($n = 264$)	6 months ($n = 218$)	12 months ($n = 103$)	Overall ($n = 264$)
Event-free	95.1%	89%	79.6%	78%
Myocardial infarction	0.76%	0.92%	0.97%	2.7%
CABG	0.34%	0.92%	1.9%	1.5%
TVR	2.3%	5%	9.7%	9.8%
TLR	0.76%	2.3%	6.8%	4.2%
Remote revascularisation	1.9%	4.1%	7.8%	8.7%
Stroke	0%	0%	0.97%	0.38%
Cardiovascular death	0%	0%	1.9%	0.76%

CABG, coronary artery bypass graft; TLR, target lesion revascularisation; TVR, target vessel revascularisation.

clinical observation ended for all patients at the same time (on 30 April 2005), the follow-up period varied from a minimum of 4 months to a maximum of more than 20 months, with a mean clinical follow-up duration of 10.5 ± 4.2 months. During follow-up, clinical data were collected in 97% of the treated patients ($n = 264$).

At 3-month follow-up, 251 of the 264 patients (95.1%) were event-free, two patients (0.76%) had MI, one patient underwent CABG (0.34%), six patients had TVR (2.3%), two patients had TLR (0.76%), and two patients had target vessel failure. Five patients (1.9%) underwent remote revascularisation for underestimated lesions at index procedure. No stroke or death occurred during this period.

At 6-month follow-up, complete for 218 patients, 89% were event-free. Two patients had MI (0.92%), two patients underwent CABG (0.92%), 11 patients had TVR (5%), five patients had TLR (2.3%), and nine patients (4.1%) had remote revascularisation for progression of CAD. No stroke or death occurred. One late in-stent thrombosis occurred in a 47-year-old male patient with multiple risk factors, previous MI and multivessel disease who underwent PCI for unstable angina. He was treated with a single PES (3 × 16 mm) in the proximal CX and only-balloon PCI at the distal segment of the same vessel. After discontinuation of double antiplatelet therapy with ticlopidine (6 months after the procedure), he had an acute MI with angiographic evidence of in-stent thrombosis in the proximal CX. Repeat only-balloon PCI was performed successfully and he was put on double antiplatelet therapy with acetylsalicylic acid and clopidogrel for 1 year. No other events were observed in this patient.

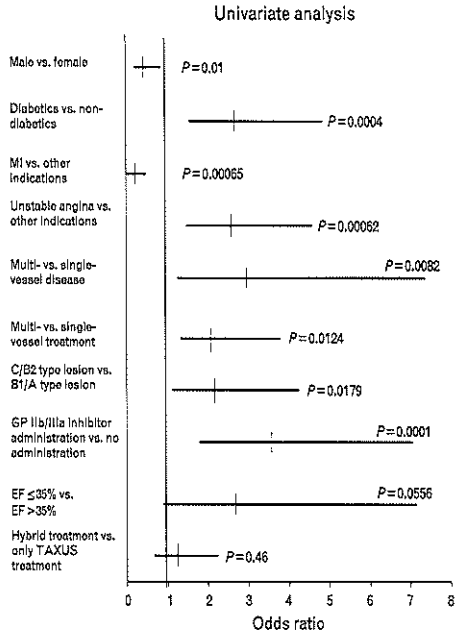
At 12-month follow-up, complete for 103 patients, 79.6% were event-free, one patient (0.97%) had MI, one patient (0.97%) had stroke, two patients underwent CABG (1.9%), 10 patients had TVR (9.7%), seven of which were TLR (6.8%), and eight patients (7.8%) underwent remote revascularisation for progression of CAD. In this period, cardiac death occurred in two patients (1.9%).

During the whole clinical follow-up period (closed on April 2005, mean follow-up 10.5 ± 4.2 months), 78% of all treated patients were event-free; overall clinical event rates were the following: MI 2.7% (seven patients), stroke 0.38% (one patient), CABG 1.5% (four patients), TVR 9.8% (26 patients), TLR 4.2% (11 patients), remote revascularisation 8.7% (23 patients). Death occurred in four patients (1.5%), two of which (0.76%) were cardiac deaths.

Univariate analysis

At univariate analysis (Fig. 1), the following characteristics were statistically associated with a significant increase in MACE incidence: female gender (OR 0.43; 95% CI 0.22–0.86; $P = 0.014$), diabetes (OR 2.73; 95% CI 1.53–4.87; $P = 0.0004$), unstable angina (OR 2.60; 95% CI 1.47–4.60; $P = 0.00062$), multivessel disease (OR 3.04; 95% CI 1.29–7.39; $P = 0.0082$), multivessel treatment (OR 2.09; 95% CI 1.16–3.77; $P = 0.0124$), type B2/C lesions (OR 2.18; 95% CI 1.13–4.20; $P = 0.0179$) and, surprisingly, use of glycoprotein IIb/IIIa inhibitors (OR 3.58; 95% CI 1.82–7.08; $P = 0.0001$). The latter might be ascribed to the more complex clinical and angiographic pattern of those patients who received glycoprotein IIb/IIIa inhibitors during the index procedure, more commonly affected by diabetes and with multivessel and diffuse disease.

Fig. 1

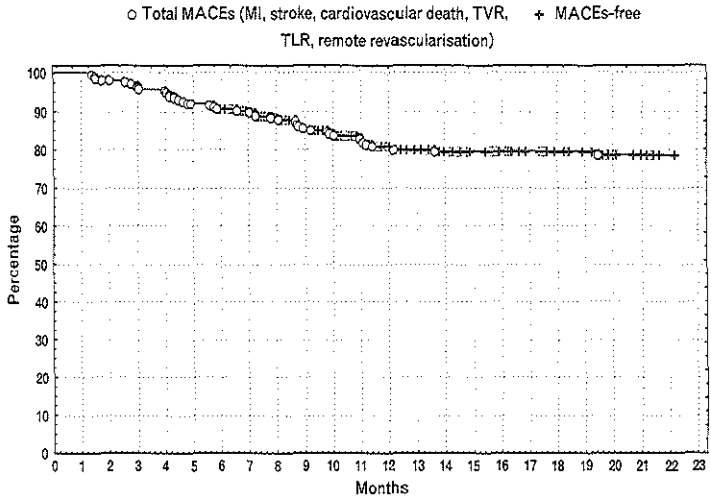


Univariate analysis: correlations between clinical, anamnestic, and angiographic characteristics and recurrence of major adverse cardiac events during follow-up. EF, ejection fraction; GP, glycoprotein; MI, myocardial infarction.

Event-free survival

Event-free survival curves (Figs 2 and 3) show that the incidence of MACEs diminished after the first year following the index procedure. The majority of MACEs occurred within the first year of the procedure, and all TLRs occurred within 11 months, with a higher incidence between the third and eighth month.

Fig. 2

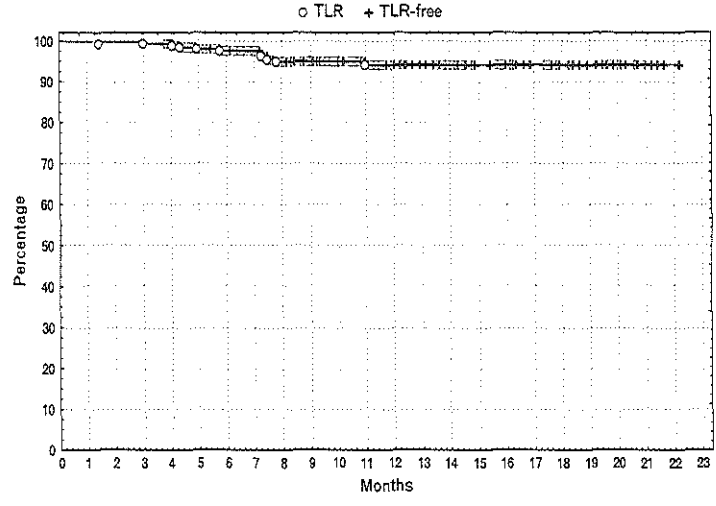


Major adverse cardiac event (MACE)-free survival. MI, myocardial infarction; TLR, target lesion revascularisation; TVR, target vessel revascularisation.

Discussion

As widely reported in the literature [16–23,25–28], the use of drug-eluting stents seems to be very effective in facing restenosis after PCI. One of the drug-eluting stents introduced into clinical practice is the PES (TAXUS Express2). At present, several randomised studies have demonstrated the safety and efficacy of the TAXUS stent in preventing restenosis as compared to bare-metal stents [21,22,25,26,28], though these results have often been obtained in strictly selected populations that have not

Fig. 3



Target lesion revascularisation (TLR)-free survival.

included patients with complex clinical presentation and angiographic patterns. In a context of great expectations, but also of relative caution, the present study aims at evaluating the safety and efficacy of PESs when used in clinical practice in an unselected 'real-world' population, including patients with a high cardiovascular risk profile and complex lesions.

The population screened in this study included a large number of patients with multiple cardiovascular risk factors, patients with previous CABG and/or PCI, patients with multivessel disease and with type B2/C lesions as well as a considerable proportion of diabetics (34.8%). Despite the complexity of the treated population, our results are absolutely consistent with the data reported in previous randomised trials. The procedural success in all patients and the low rate of procedural and in-hospital complications confirm the safety of this device. The results obtained in this study are in keeping with those reported in the TAXUS IV trial [27] (TVR 9.8 vs. 7.1% in TAXUS IV; TLR 4.2 vs. 4.4% in TAXUS IV). Moreover, since most of MACEs were due to progression of coronary atherosclerosis (remote revascularisation), these results should be considered very encouraging. Similar outcomes were also reported in the TAXUS VI trial [28].

As confirmed by a TAXUS IV trial subgroup study [29], univariate analysis pointed out that diabetic patients have a higher risk of MACEs during follow-up if compared to non-diabetic ones. In that series of patients, Hermiller *et al.* [29] suggested the superiority of PESs (TAXUS) for the treatment of diabetic patients as compared to sirolimus-eluting stents, albeit this superiority was not confirmed in a recent randomised study [30]. Female gender as well as multivessel disease patients and complex lesion morphology (type B2/C) have always been considered at higher risk for restenosis when treated by conventional stents. Also in the present study, a higher incidence of MACEs was observed in these subgroups of patients, as previously reported by Lansky *et al.* [31]. However, if compared to historical data on bare-metal stents, PESs in these patient subsets have significantly improved clinical outcome.

With respect to drug-eluting stent use, the scientific community has often been concerned with the major risk of acute and subacute in-stent thrombosis due to delayed in-stent endothelialisation as a result of the drug antiproliferative effects. This is also the reason why double antiplatelet therapy is recommended for at least 6 months after PES implantation. Despite the complexity of the patients treated, the in-stent thrombosis rate observed in this study was extremely low and similar to that reported in previous randomised trials. These results confirm the safety and efficacy of this device also in an unselected and complex population, even if this issue warrants further evaluation in ad-hoc designed studies.

Study limitations

The major limitation of this investigation is that these findings are based on a single-centre observational study and the number of enrolled patients is relatively small to generalise our results to all patients treated with PESs. However, our study population represents the so-called 'real-world' patients who are daily treated regardless of inclusion or exclusion criteria. Despite a relative caution, such studies provide relevant safety and efficacy data on PESs when used in clinical practice, in high-risk patients with complex lesions who are usually excluded from randomised trials.

Moreover, the present study is lacking an angiographic follow-up; in fact, only patients with clinical symptoms or instrumental signs of ischaemia underwent angiographic control. However, data deriving from previous randomised trials that scheduled an angiographic follow-up indicate that clinical outcomes are strictly related to the angiographic ones; therefore, it can be hypothesised that the low clinical event rate observed is likely to match with an equally low angiographic event rate. Consequently, it could be argued that the encouraging clinical outcome in this series of patients may correspond to an effective control of angiographic restenosis.

In conclusion, the present study demonstrates that PCI with PES implantation is safe and effective also in an unselected population with a high cardiovascular risk profile associated with complex coronary lesions.

References

1 Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS. Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy. *J Am Coll Cardiol* 1993; **21**:15–25.

2 Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, *et al.* A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med* 1994; **331**:489–495.

3 Topol EJ, Leya F, Pinkerton CA, Whitlow PL, Hofling B, Simonton CA, *et al.* A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease. The CAVEAT Study Group. *N Engl J Med* 1993; **329**:221–227.

4 Baim DS, Cutlip DE, Sharma SK, Ho KK, Fortuna R, Schreiber TL, *et al.* Final results of the Balloon vs. Optimal Atherectomy Trial (BOAT). *Circulation* 1998; **97**:322–331.

5 Cutlip DE, Chauhan MS, Baim DS, Ho KK, Popma JJ, Carrozza JP, *et al.* Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. *J Am Coll Cardiol* 2002; **40**:2082–2089.

6 Mehran R, Mintz GS, Satler LF, Pichard AD, Kent KM, Bucher TA, *et al.* Treatment of in-stent restenosis with excimer laser coronary angioplasty: mechanisms and results compared with PTCA alone. *Circulation* 1997; **96**:2183–2189.

7 Kastor R, Hamm CW, Seabra-Gomes R, Herrmann G, Siovert H, Macaya C, *et al.* Laser angioplasty of restenosed coronary stents: results of a multicenter surveillance trial. The Laser Angioplasty of Restenosed Stents (LARS) Investigators. *J Am Coll Cardiol* 1999; **34**:25–32.

8 Albiero R, Silber S, Di Mario C, Cornigliaro C, Battaglia S, Reimers B, *et al.* Cutting balloon versus conventional balloon angioplasty for the treatment of in-stent restenosis: results of the Restenosis Cutting Balloon Evaluation Trial (RESCUT). *J Am Coll Cardiol* 2004; **43**:943–949.

9 Adamian M, Colombo A, Briguori C, Nishida T, Marsico F, Di Mario C, *et al.* Cutting balloon angioplasty for the treatment of in-stent restenosis: a matched comparison with rotational atherectomy, additional stent implantation and balloon angioplasty. *J Am Coll Cardiol* 2001; **38**:672–679.

10 Bhargava B, Karthikeyan G, Abizaid AS, Mohran R. New approaches to preventing restenosis. *BMJ* 2003; **327**:274–279.

11 Verin V, Popowski Y, de Bruyne B, Baumgart D, Sauerwein W, Lina M, *et al.* Endoluminal beta-radiation therapy for the prevention of coronary restenosis after balloon angioplasty. The Dose-Finding Study Group. *N Engl J Med* 2001; **344**:243–248.

12 Leon MB, Teirstein PS, Moses JW, Tripuraneni P, Lansky AJ, Jani S, *et al.* Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. *N Engl J Med* 2001; **344**:250–256.

13 Waksman R, Raizner AE, Yeung AC, Lansky AJ, Vandertie L, Use of localised intracoronary beta radiation in treatment of in-stent restenosis: the INHIBIT randomised controlled trial. *Lancet* 2002; **359**:551–557.

14 Babapulle MN, Eisenberg MJ. Coated stents for the prevention of restenosis: part I. *Circulation* 2002; **106**:2734–2740.

15 Serruys PW, van Hout B, Bonnier H, Legrand V, Garcia E, Macaya C, *et al.* Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* 1998; **352**:673–681.

16 Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, *et al.*, for the SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; **349**:1315–1323.

17 Sousa JE, Costa MA, Abizaid AC, Rensing BJ, Abizaid AS, Tanajura LF, *et al.* Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation* 2001; **104**:2007–2011.

18 Lüstre F, Stankovic G, Di Mario C, Takagi T, Chieffo A, Moshiri S, *et al.* First clinical experience with a paclitaxel derivate-eluting polymer stent system implantation for in-stent restenosis: immediate and long-term clinical and angiographic outcome. *Circulation* 2002; **105**:1883–1886.

19 Park SJ, Shim WH, Ho DS, Raizner AE, Park SW, Hong MK, *et al.* A paclitaxel-eluting stent for the prevention of coronary restenosis. *N Engl J Med* 2003; **348**:1537–1545.

20 Gershlick AH, Deschaorder I, Chevalier B, Camenzind E, Gommeaux A, Vrints C, *et al.* Local drug delivery to inhibit coronary artery restenosis. Data from the ELUTES (Evaluation of Paclitaxel Eluting Stent) clinical trial (abstract). *Circulation* 2001; **104**:II416.

21 Grube E, Silber S, Hauptmann KE, Mueller R, Buellesfeld L, Gerckens U, *et al.* TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation* 2003; **107**:38–42.

22 Tanabe K, Serruys PW, Degertekin M, Guagliumi G, Grube E, Chan C, *et al.*, for the TAXUS II Study Group. Chronic arterial responses to polymer-controlled paclitaxel-eluting stents. Comparison with bare metal stents by serial intravascular ultrasound analyses: data from the randomized TAXUS-II trial. *Circulation* 2004; **109**:196–200.

23 Serruys PW, Degertekin M, Tanabe K, Russell ME, Guagliumi G, Webb J, *et al.*, for the TAXUS II Study Group. Vascular responses at proximal and distal edges of paclitaxel-eluting stents: serial intravascular ultrasound analysis from the TAXUS II trial. *Circulation* 2004; **109**:627–633.

24 Tanabe K, Serruys PW, Degertekin M, Grube E, Guagliumi G, Urbaszek W, *et al.*, for the TAXUS II Study Group. Incomplete stent apposition after implantation of paclitaxel-eluting stents or bare metal stents: insights from the randomized TAXUS II trial. *Circulation* 2005; **111**: 900–905.

25 Tanabe K, Serruys PW, Grube E, Smits PC, Selbach G, van der Giessen WJ, *et al.* TAXUS III trial: in-stent restenosis treated with stent-based delivery of paclitaxel incorporated in a slow-release polymer formulation. *Circulation* 2003; **107**:559–564.

26 Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, *et al.*, for the TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004; **350**:221–231.

27 Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, *et al.*, for the TAXUS-IV Investigators. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation* 2004; **109**:1942–1947.

28 Dawkins KD, Grube E, Guagliumi G, Banning AP, Zmudka K, Colombo A, *et al.*, for the TAXUS VI Investigators. Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice. *Circulation* 2005; **112**:3306–3313.

29 Hermiller JB, Raizner A, Cannon L, Gurbel PA, Kutcher MA, Wong SC, *et al.*, for the TAXUS-IV Investigators. Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: the TAXUS-IV trial. *J Am Coll Cardiol* 2005; **45**:1172–1179.

30 Dibra A, Kastrati A, Mehilli J, Pache J, Schühlen H, von Beckerath N, *et al.*, for the ISAR-DIABETES Study Investigators. Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med* 2005; **353**:663–670.

31 Lansky AJ, Costa RA, Mooney M, Midei MG, Lui HK, Strickland W, *et al.* Gender-based outcomes after paclitaxel-eluting stent implantation in patients with coronary artery disease. *J Am Coll Cardiol* 2005; **45**: 1180–1185.

CHAPTER 14

SHORT- AND LONG-TERM OUTCOMES OF PERCUTANEOUS CORONARY INTERVENTIONS IN PATIENTS WITH SEVERE LEFT VENTRICULAR DYSFUNCTION

EuroIntervention

Short- and long-term outcomes of percutaneous coronary interventions in patients with severe left ventricular dysfunction

Imad Sheiban[1]*, MD; Claudio Moretti[1], MD; Giuseppe Biondi Zoccai[1], MD; Giuseppe M.C. Rosano[2], MD, PhD; Filippo Sciuto[1], MD; Walter Grosso Marra[1], MD; Emanuele Meliga[1], MD; Alison Fumagalli[1], MD; Gianpaolo Ballari[1], MD; Serena Beninati[1], MD; Pierluigi Omedè[1], MD; Gian Paolo Trevi[1], MD

1. Interventional Cardiology, Division of Cardiology, University of Torino, San Giovanni Battista Hospital, Torino, Italy; 2. Cardiovascular Research Unit, San Raffaele Hospital, Rome, Italy

The authors have no conflict of interest to disclose.

KEYWORDS
Coronary artery disease, heart failure, percutaneous coronary intervention

Abstract

Aims: Poor left ventricular function is considered a high risk condition for performing either percutaneous (PCI) or surgical revascularisation. The aim of this study was to evaluate immediate and long term results of PCI in patients with coronary artery disease (CAD) and severe left ventricular dysfunction (EF ≤0.30).

Methods and results: Seventy-eight consecutive patients with CAD and severe left ventricular dysfunction (EF ≤30%) were selected. The majority of these patients (87%) had multivessel disease. Coronary angioplasty procedure was mainly motivated by angina associated with clinical manifestation of heart failure (54%). Total number of treated vessels was 181, and a total of 203 stents were implanted (2.6 stent/patient). Procedural success was achieved in 77 patients (97.8%). The total procedural and in-hospital adverse event rate was 7.8%. Mean follow-up period (FU) was 25±6 months. Event-free survival rate at the end of FU was 55%; repeat revascularisation was performed in 21 patients (27.6%). Female gender, diabetes, new acute myocardial infarction and number of treated vessels were independent predictors for death and combined mayor adverse cardiac events (MACE) during the follow-up.

Conclusions: In symptomatic patients with CAD and severe left ventricular dysfunction, PCI can be performed with excellent procedural outcome and acceptable long-term morbidity and mortality.

* *Corresponding author: Cardiac Catheterisation and Interventional Cardiology, Division of Cardiology, University of Torino, San Giovanni Hospital, Corso Bramante 88-90, 10126 Torino, Italy*
E-mail: ishelban@yahoo.com

Introduction

Severe left ventricular dysfunction in patients with coronary artery disease is often, but not always, the consequence of an acute myocardial infarction or an ischaemic cardiomyopathy[1]. It is estimated that most patients with severe left ventricular dysfunction, undergoing heart transplantation, might have areas of hibernated myocardium and could benefit from myocardial revascularisation[2]. Even symptomatic patients are often denied appropriate interventional treatment due to fear of procedural failure and are maintained on heavy medical therapy, the fortunate few receiving cardiac transplantation. Such patients have very limited survival when treated medically[3-4] and usually die of cardiac causes related to recurrent ischaemia or infarction, cardiac heart failure or ventricular arrhythmias.

In patients with ischaemic dilated cardiomyopathy, myocardial revascularisation is highly indicated when myocardial viability is documented by non-invasive tests (dobutamine stress echocardiography, thallium 201 scintigraphy, PET). However, it must be also underlined that poor left ventricular function, *per se*, is considered a high risk condition for either percutaneous or surgical coronary revascularisation[5]. The clinical benefit of percutaneous coronary interventions (PCI) in such patients is not well established. The aim of the present study was to evaluate immediate and long-term procedural and clinical outcome of PCI in patients with obstructive coronary disease (mostly multivessel) and severe left ventricular dysfunction (EF <30%).

Methods

Study group

Between January 2000 and December 2001, from the patients undergoing percutaneous coronary interventions in our centre after having performed myocardial viability studies, we selected 78 consecutive patients with documented coronary artery disease, severe left ventricular dysfunction (EF≤30%) and evidence of viable myocardium. Indication for coronary angiography were made by the referring physician on the basis of chest pain and/or cardiac failure manifestations. Indications for PCI were made by the attending physician after having reviewed the coronary angiography and the results of myocardial viability studies. Myocardial viability was documented in all patients by SPECT and/or by dobutamine stress echocardiography. Left ventricular ejection fraction was assessed by transthoracic echocardiogram (using a planimetric method) and by left ventriculography at the time of diagnostic angiography.

Cardiac catheterisation

Diagnostic coronary angiography was performed in all patients to assess left ventricular function and the presence and extent of coronary artery disease. The left ventricular ejection fraction was estimated by a single-plane 35°RAO ventriculogram. PCI was performed in all patients. Intention to treat was for complete revascularisation by PCI in all patients. Procedural and in-hospital events were monitored in all.

Long-term clinical follow-up

Patients were followed with out-patient visits after one, three and every six months or by phone interviews. At each visit, health status was assessed by a complete cardiac evaluation, including echocardiogram, when needed. An echocardiogram for the assessment of regional and global left ventricular function was performed routinely at discharge and at six months after PCI. Non-fatal and fatal cardiac events were documented either by hospital charts or by coroner's reports. Mean follow-up period was 28±6 months (range: 22 to 39 months) and was completed in 92.3% (72/78 patients). The following events were recorded during follow-up: 1) cardiac and non-cardiac death, 2) recurrent symptoms, 3) recurrent ischaemic events (myocardial infarction non-Q and Q-AMI), 4) congestive heart failure, 5) need for revascularisation (re-PCI or CABG). EF on transthoracic echocardiography was also evaluated.

Statistical analysis

Data are expressed as mean±SD or as percentage where appropriate. Multivariate analysis was performed using a Cox proportional hazard model to assess predictor clinical factors of long term outcome. A p value of less than 0.05 was considered significant. The following variables were entered in the multivariate analysis: age, sex, coronary risk factors, extent of coronary artery disease, left ventricular function, complete/incomplete revascularisation, peri-procedural cardiac enzyme release previous myocardial infarction, previous CABG, previous PCI.

Results

Demographic and clinical characteristics of study patients are shown in Table 1. The majority of patients (71%) were males, mean age was 64±7 years with 27 patients having more than 65 and nine more than 75 years. Hypertension, diabetes, hypercholesterolaemia, a history of smoking and a family history of coronary artery disease

Table 1. Demographic and clinical characteristics.

No. Patients=78	
Age	64±7
Sex: male/female	55/23
Distribution of coronary risk factors:	
Hypercholesterolaemia	62%
Hypertension	56%
Diabetes mellitus	28%
Cigarette smoking	58%
Family history	47%
Previous AMI	53%
Previous PCI	19%
Previous CAGB	23%
Only angina	37%
Angina associated with clinical manifestations of CHF	54%
Positive inducible ischaemia or myocardial viability	9%
Adjunctive medical therapy	
ACE inhibitors	100%
Beta Blockers	58%
Statins	68%

were common, 36 patients (53%) had experienced a previous Q wave or non-Q myocardial infarction. Thirty-three patients (42%) had undergone a previous myocardial revascularisation: 15 (19%) by PCI and 18 (23%) by coronary artery bypass surgery (CABG). All patients were on medical therapy with ACE-inhibitors, 58% were also receiving beta blockers and 68% of patients were on statins. Double anti-platelet therapy (ASA + clopidogrel or ticlopidine) was continued for at least one month following the procedure in all patients.

Clinical indications for PCI procedure were mostly represented by angina and/or heart failure manifestations: 29 patients had only angina and 42 patients had angina associated with congestive heart failure manifestation, in seven patients PCI procedure was performed on the basis of the worsening of left ventricular function associated with a positive non-invasive test for inducible ischaemia or myocardial viability. Left ventricular EF was 25±2% ranging from 23 to 28%.

Angiographic characteristics are summarised in Table 2. Ten patients (13%) had single vessel disease and 68 (87%) had multivessel disease. All 18 patients with previous CABG had multivessel disease with at least one venous graft disease.

Procedural and in-hospital outcomes

All patients received IIb/IIIa antagonists prior to procedure. In 36 patients (47%) intra-aortic balloon contra-pulsation was used during the PCI procedure. Complete revascularisation by PCI was attempted in all patients with 181 vessels treated (2.3 vessel/ patient), 23% of treated vessel were left anterior descending arteries, 8% were left main, 9% were diagonal branches, 17% were left circumflex arteries, 10% were marginal branches, 22% were right coronary arteries, 10% were posterior descending or postero-lateral branches and 6% were saphenous vein grafts (Table 2). Multivessel PCI was performed in 88% of patients. Multiple stent implantation was used in 76% of patients. Debulking before stent implantation by directional atherectomy was performed in 4% of patients. In two patients, rotational ablation atherectomy was needed because of heavily calcified lesions. A total of 203 stents were implanted (2.6 stent /patient, 1.1 stent / vessel) .

Technical procedural success was obtained in 98.7% of patients. Procedural death occurred in one patient (1.3%), non Q-AMI in three patients (3.9%), stroke in one patient (1.3%), emergency CABG was not needed in any case. One death occurred two weeks following the procedure for acute renal failure. No other complication were observed. Thus total procedural and in-hospital major adverse cardiac events were 7.7% (Table 3).

Table 2. Angiographic and procedural data.

No. patients = 78		
– Single vessel disease	10	(12.8%)
– Multivessel disease	68	(87.2%)
No. Treated vessels=181		
LMCA	12	(7%)
Protected	8	
Unprotected	4	
LAD	41	(23%)
Diagonal	17	(9%)
LCX	28	(16%)
Marginal	19	(10%)
RCA	40	(22%)
PDA-PL	16	(9%)
SVG	8	(4%)
No. treated lesions	243	3.1 lesions/patient
No. stents implanted	203	2.6 stent /patient
		1.1 stent/vessel
Multivessel PCI	68	87%
Debulking prior stenting		
DCA	3	3.9%
ROTA	2	2.6%
GP IIb /IIIa inhibitors	78	100%
Intra-aortic balloon contra-pulsation	36	47%

LMCA: left main coronary artery; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; PDA: posterior descending artery; PL: postero-lateral branch; SVG: saphenous vein graft DCA: directional coronary atherectomy; ROTA: rotation-ablation atherectomy

Table 3. Procedural and in-hospital outcome.

No. patients=78		
Procedural success	77	(98.7%)
Death	1	(1.3%)
Non Q-AMI	3	(3.9%)
Q-AMI	0	
Stroke	1	(1.3%)
Emergent CABG	0	
In-Hospital death	1	(1.3%)

CABG: coronary artery bypass grafting; AMI; acute myocardial infarction

Clinical follow-up

During a mean follow up of 25±6 months 42 patients (55%) had event-free survival. Nine patients (11.8%) died: seven (9.2%) cardiac, and two (2.6%) non-cardiac. Cardiac death was caused by left heart failure in three patients, ischaemic events in two patients and ventricular fibrillation in two patients. Sixteen patients (21%) had recurrence of angina, while four patients (5.3%) had new MI (three non-Q, and one Q-AMI) and five patients (6.6%) were hospitalised because of congestive heart failure. All 20 patients (26.3%) with recurrent angina or AMI required a repeat PCI. Thus, total major adverse cardiac events during the follow up were 44.7%, mainly represented by the need for repeat revascularisation. In 39 patients, left ventricular function assessed by echocardiography improved at six months from 25±2% to 39±5%, $p< 0.001$. In the remaining 37 patients, left ventricular ejection fraction was unchanged (basal conditions 26±4 vs 6-month follow-up 28±5, ns). Female gender, the presence of diabetes mellitus, previous CABG, new AMI, unchanged EF at six months following the procedure and the number of treated vessels were significantly predictors of death during follow-up.The same parameters were also significant predictors for combined major adverse cardiac events during follow-up (Table 4).

Table 4. Predictor clinical factors of long-term outcome (multivariate analysis).

	RR	CI	value
Death			
Diabetes	1.06	(1.42-1.02)	<0.01
Female Gender	1.41	(2.82-1.16)	<0.01
Hypertension	1.36	(2.02-0.64)	NS
Hypercholesterolaemia	1.54	(2.56-0.97)	NS
Cigarette smoking	1.31	(2.06-0.38)	NS
Family history	0.81	(1.97-0.22)	NS
Chronic stable angina	0.64	(1.95-0.43)	NS
Previous AMI	1.23	(1.89-0.76)	NS
New AMI	1.18	(1.65-1.10)	<0.001
Previous CABG	1.26	(1.92-1.01)	<0.05
Previous PCI	1.37	(1.98-0.45)	NS
Unchanged EF a 6 months	1.31	(154-1.02)	<0.01
No. of treated vessels	1.42	(2.12-1.45)	<0.01
Combined MACE			
Diabetes	1.57	(3.16-1.18)	<0.001
Female Gender	1.62	(2.78-1.16)	<0.01
Hypertension	0.9	(1.56-0.45)	NS
Hypercholesterolaemia	1.35	(2.55-0.98)	NS
Cigarette smoking	1.17	(2.11-0.78)	NS
Family history	0.93	(1.76-0.68)	NS
Previous AMI	1.35	(2.92-1.05)	<0.05
Previous CABG	1.34	(2.59-1.11)	<0.05
Previous PCI	1.12	(2.65-0.84)	NS
New AMI	1.48	(3.12-1.23)	<0.001
Unchanged EF at 6 months	1.55	(2.43-1.12)	<0.01
No of treated vessels	1.56	(2.961.28)	<0.01

CABG:coronary artery bypass grafting; AMI: acute myocardial infarction; CHF: cardiac heart failure; Re-PCI: repeat percutaneous coronary interventions; New AMI: acute myocardial infarction occurred during the procedure, in-hospital or follow-up period.

Table 5. Long-term clinical follow-up (range: 22 to 39 months; mean=28±6 months).

Clinical follow-up: range 18 t0 34 months (mean 25 ±6 months)		
Number of patients	76	
Death	9	(11.8%)
Cardiac	7	(9.2%)
Non-cardiac	2	(2.6%)
Recurrent symptoms	28	(36.8%)
Angina	16	(21%)
Non Q-AMI	3	(3.9%)
Q-AMI	2	(2.6%)
CHF	7	(9.2%)
Repeat revascularisation	21	(27.6%)
RE-PCI	19	
CABG	2	
Total MACE during follow-up	34	(45%)
Event-free survival	42	(55%)
Total survival	67	(88.2%)

CABG: coronary artery bypass grafting; AMI: acute myocardial infarction; CHF: cardiac heart failure; Re-PCI: repeat percutaneous coronary interventions

Discussion

Immediate and long-term prognosis of patients with ischaemic cardiomyopathy following myocardial revascularisation (both mechanical or surgical) have been investigated in few studies, and among these the majority were undertaken many years ago when technological and medical treatments were different from the ones available at the present time (Table 5)[5-11].

Technical advances in the field of interventional cardiology with the introduction of coronary stents and potent antiplatelet therapies have resulted in a marked increase in the complexity of procedures and expanded indications, even in patients considered as high-risk, like those included in the present study. One of the striking findings of this study is the safety of PCI as well as the favourable long term outcome in patients with severe left ventricular dysfunction due to coronary artery disease. This is in contrast with the data recently reported by Keelan at al from the DYNAMIC Registry[12] where there was an observed increased in-hospital MACE (including mortality) in patients with left ventricular ejection fraction < 40 undergoing PCI. This discrepancy might be due to several factors: the Registry included patients recruited in 10 different sites, GP IIb/IIIa inhibitors were used in only 24% of patients and it was not mentioned if intra-aortic balloon contra-pulsation was used while in the present study IIb/IIIa inhibitors were used in all patients and in almost half of patients intra-aortic balloon contra-pulsation was employed during the procedure.

Medical treatment for patients with severe left ventricular function and coronary artery disease is associated with poor prognosis. Luciani and colleagues reported 28%, five year survival in 72 patients with an average EF of 21%[4]. However, medical treatment have also been markedly improved over the last decade. Although many questions remain in attempting to optimise the management for these patients, myocardial revascularisation seems to offer some advantages.

The BARI study showed a seven year survival after PTCA in patients with reduced left ventricular function (EF<50%) and two vessel disease of 78%[13]. The same study provided evidence that there was no significant differences in seven year survival in an initial strategy of PTCA or CABG among non-diabetic patients with three-vessel disease, and among all patients with two-vessel disease involving the proximal left anterior descendent artery. The authors suggested that PTCA may be offered to such patients as an initial revascularisation without compromising the seven year survival.

Hasdai and colleagues, reported among 611 patients undergoing PCI a higher 10 year mortality in patients with left ventricular dysfunction (EF<40%) compared to those with normal systolic function (47% vs 20%; p<0,0001)[14].

In a recent study by Li et al[15], 74 patients with ejection fraction < 40% underwent percutaneous coronary angioplasty, including 61 with stent back-up. During long-term follow up (29±23 months), 58 (87.9%) of 66 patients with clinical success were alive, including 44 (68.6%) free from cardiac events. In the present study, total survival at 25±6 months was 88.2% (with an event-free survival 55%), similar to that reported in the previous studies, despite a more severe left ventricular dysfunction (EF < 30%) than those reported in those studies[13-15].

Recent reports suggest that approximately 50% of patients with ischaemic cardiomyopathy have viable myocardium, and 25% of

these have sufficient amounts of viable myocardium resulting in a functional improvement (increased left ventricular ejection fraction, increased exercise capacity) following myocardial revascularisation[16-18]. Improved functional status and symptoms after revascularisation, even with limited preoperative assessment of myocardial viability, has been reported by Christian et al[17].

All patients included in the present study had documented viable myocardium, but only 39 patients showed a significant improvement of ejection fraction at six months following the procedure. Improvement in left ventricular function after PCI is an important predictor of long-term outcome. Multivariate analysis showed that unchanged EF at follow-up was significantly associated with increased cardiac death and MACE. Worsening of left ventricular function related to new myocardial damage, either by intraprocedural AMI or occurring during follow-up, were also significant predictors for death and MACE. Multivessel PCI as well as diffuse disease are often associated with slight increases of cardiac enzymes, and this may be the cause of greater occurrence of cardiac events in diabetics and in patients with complex lesions and side-branch involvement. The loss of even small amounts of viable myocardium in these patients adds a further myocardial damage and might negatively influence long-term clinical outcome as shown by multivariate analysis.

Taking into account these considerations, long-term clinical outcome is acceptable considering the natural history in this patient subset. Total survival at >2 years is excellent, although only 50% may benefit from PCI procedures with event-free survival. The key for a favourable long-term clinical outcome seems to be the recovery in left ventricular function, but unfortunately this cannot always be predicted by myocardial viability tests. All patients included in the present study had positive test, but only 53% had improvement of EF. On the other hand, it has been reported that myocardial revascularisation might improve functional capacity in patients with left ventricular dysfunction and negative myocardial viability test[19,20]. Incomplete revascularisation was not associated with unfavourable outcome. In this series, revascularisation was limited to vessels supplying areas with documented viable myocardium, thereby suggesting that in most cases an incomplete revascularisation may benefit patients with left ventricular dysfunction if PCI is performed on the vessel targeted by the viability study. Caution should be made in patients selection; those with diffuse and complex coronary lesions are at higher risk for procedural complications, especially biomarker elevations following procedure must be carefully evaluated. Complex procedures associated with biomarker elevations might even worsen long-term clinical outcome in these patients.

Another important finding of this study is that long-term mortality remains high, even after successful coronary intervention. We found an overall mortality of 11% at 24 month follow-up, compared to 6% in the study by Di Sciascio[21]. However, patients in our study had more frequent diabetes (28% versus 14%), more prior CABG (23% versus 6%), and more multivessel coronary disease (87% versus 54%). The mortality of 11% at 24-month follow-up in our study compares favourably to the 15-25% mortality rate at two- to three-year follow-up reported in the angioplasty era.

Study limitations

This is a non-randomised, retrospective, observational study with the all the inherent limitations of such a trial. There is no control group, however, it is well documented that prognosis in this subgroup of patients (EF<0.30) is very poor, even over a short time period. Event-free survival of 55% after a time period of 25±8 months could be considered poor, but the main component of major cardiac events during the follow up period was recurrence of angina and repeat revascularisation. It could be speculated that better results might be obtained with the use of drug-eluting stents. Finally, all patients included in this study were on treatment with ACE-inhibitors, and the majority were also treated with statins (68%) and beta blockers (58%), and this might influence clinical outcome.

In conclusion, PCI in patients with severe left ventricular dysfunction and documented viability can be performed with excellent procedural and in-hospital outcome in those patients with severe ischaemic left ventricular dysfunction and evidence of viable myocardium. Predictors for unfavourable long-term outcome are represented by female gender, the presence of diabetes, extent of coronary disease, lack of recovery in left ventricular function and new episodes of myocardial infarction. In some of these patients, PCI and repeat procedures represent the only therapeutic option. In addition, in carefully selected subgroups of patients with severe left ventricular dysfunction and coronary artery disease, PCI may be considered as an alternative or a "bridge" approach for cardiac transplantation.

References

1. Bourassa MG, Gurné O, Bangdiwala SI, Ghali JK, Young JB, Rousseau M, Johnstone DE, Yusuf S. Natural history and patterns of current practice in heart failure. *J Am Coll Cardiol.* 1993;22 (suppl A):14A-19A.

2. Gheorghiade M, Bonow RO. Chronic heart failure in the United States. A manifestation of coronary artery disease. *Circulation* 1998; 97: 282-9.

3. Beanlands RS, Hendry PJ, Masters RG, deKemp RA, Woodend K, Ruddy TD. Delay in revascularization is associated with increased mortality rate in patients with severe left ventricular dysfunction and viable myocardium on fluorine 18-fluorodeoxyglucose positron emission tomography imaging. *Circulation* 1998; 98: 51-6.

4. Luciani GB, Faggian G, Razzolini R, Livi U, Bortolotti U, Mazzucco A. Severe ischemic left ventricular failure: coronary operation or heart transplantation? *Ann Thorac Sur* 1993;55:719-723.

5. Hartzler GO, Rutherford BD, McConahay DR, Johnson WL, Giorgi LV. High risk percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1988; 61(14) 33G-37G.

6. Stevens T, Kahn JK, McCallister BD, Ligon RW, Spaude S, Rutherford BD, McConahay DR, Johnson WL, Giorgi LV, Shimshak TM. Safety and efficacy of percutaneous transluminal coronary angioplasty in patients with left ventricular disfunction. *Am J Cardiol* 1991;68(4):313-9.

7. Serota H, Deligonul U, Lee WH, Aguirre F, Kern MJ, Taussig SA, Vandormael MG. Predictors of cardiac survival after percutaneous transluminal coronary angioplasty in patients with severe left ventricular dysfunction. *Am J. Cardiol* 1991; 67: 367-372

8. Reynen K, Kunkel B, Gansser R, Bachmann K. Percutaneous transluminal coronary angioplasty in patients with severely depressed left ventricular function. *Cardiology* 1993;83(5-6):358-66.

9. Holmes DR Jr, Detre KM, Williams DO, Kent KM, King SB 3rd, Yeh W, Steenkiste A. Long term outcome of patients with depressed left ventricular function undergoing percutaneous transluminal coronary angioplasty. The NHLBI PTCA Registry. *Circulation* 1993;87(1):291-3.

10. Maiello L, Colombo A, Gianrossi R, Almagor Y, Finci L. Survival after percutaneous transluminal coronary angioplasty in patients with severe left ventricular dysfunction. *Chest* 1994;105(3):733-40.

11. Beurrier D, Tricoche O, Feldmann L, Juillière Y, Buffet P, Anconina J, Cherrier F, Danchin N. Transluminal coronary angioplasty in patients with left ventricular dysfunction; immediate and long-term results. *Arch Mal Coeur et Vaiss.* 1995; 88 (2): 225-30.

12. Keelan PC, Johnston JM, Koru-Sengul T, Detre KM, Williams DO, Slater J, Block PC, Holmes DR Jr; Dynamic Registry Investigators. Comparison of in-hospital and one-year outcomes in patients with left ventricular ejection fractions < 40%, 41% to 49% and > 50% having percutaneous coronary revascularization. *Am J Cardiol* 2003; 91:1168-1172.

13. Berger PB, Velianou JL, Aslanidou Vlachos H, Felt F, Jacobs AK, Faxon DP, Attubato M, Keller N, Stadius ML, Weiner BH, Williams DO, Detre KM; BARI Investigators. Survival following coronary angioplasty versus coronary artery by-pass surgery in anatomy subset in which coronary artery by-pass surgery improves survival compared with medical therapy. Results from the By-pass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol* 2001;38(5):1440-9.

14. Hasdai D, Bell MR, Grill DE, Berger PB, Garratt KN, Rihal CS, Hammes LN, Holmes DR Jr. Outcome ≥ 10 years after successful percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1997;79(8): 1005-11.

15. Li C, Jia G, Guo W, Li W. Stent supported coronary angioplasty in patients with severe ventricular dysfunction. *Chinese Medical Journal* 2002; 115 (3): 355-8.

16. Auerbach MA, Schöder H, Hoh C, Gambhir SS, Yaghoubi S, Sayre JW, Silverman D, Phelps ME, Schelbert HR, Czernin J. Prevalence of myocardial viability as detected by positron emission tomography in patients with ischemic cardiomyopathy. *Circulation* 1999;99:2921-6.

17. Christian TF, Miller TD, Hodge DO, Orszulak TA, Gibbons RJ. An estimate of the prevalence of reversible left ventricular dysfunction in patients referred for coronary bypass-surgery. *J Nucl Cardiol* 1996; 4:140-6.

18. Go RT, MacIntyre WJ, Cook SA, Neumann DR, Brunken RC, Saha GB, Underwood DA, Marwick TH, Chen EQ, King JL, Khandekar S. The incidence of scintigrafically viable and non viable tissue by rubidium-82 and fluorine-18-fluorodeoxyglucose positron emission tomographic imaging in patients with prior infarction and left ventricular dysfunction. *J Nucl Cardiol* 1996;3:96-104.

19. Sciagrà R, Leoncini M, Cannizzaro G, Marucci G, Pupi A, Bisi G. Predicting revascularization outcome in patients with coronary artery disease and left ventricular dysfunction (data from SEMINATOR Study). *Am J Cardiol* 2002,; 89: 1369-1373.

20. Shah BR, Velazquez E, Shaw LK, Bart B, O'Connor Ch, Wagner GS: Revascularization improves survival inischemic cardiomiopathy regardless of electrocardiographic citeria for prior small-to-medium myocardial infarcts. *Am Heart J* 2002; 143: 111-117.

21. Di Sciascio G, Patti G, D'Ambrosio A, Nusca A: Coronary Stenting in patirnts with depressed left ventricular function: acute and long-term results in a selected population *Catheter Cardiovasc Interv* 2003: 59: 429-433.

22. Marsico F, Morenghi E, Parenti DZ, Milone F, Maiello L, Carcagni A Scatturin M, Presbitero P: Immediate and late results of coronary angioplasty in patients with severe left ventricular dysfunction. *Ital Heart J* 2003; 4: 838-842.

23. Aslam F and Blankenship J: Coronary artery stenting in patients with severe left ventricular dysfunction. *J Invasive Cardiol* 2005; 17: 656-658.

CHAPTER 15

MAKING SENSE OF THE RECENT META-ANALYTICAL CONFUSION CONCERNING THE SAFETY OF DRUG-ELUTING STENTS

Expert review

EuroIntervention

Making sense of the recent meta-analytical confusion concerning the safety of drug-eluting stents

Giuseppe G. L. Biondi-Zoccai[1], MD; Pierfrancesco Agostoni[2], MD; Claudio Moretti[1], MD; Emanuele Meliga[1,3], MD; Imad Sheiban[1]*, MD

1. Interventional Cardiology, Division of Cardiology, University of Turin, Turin, Italy; 2. Antwerp Cardiovascular Institute Middelheim, AZ Middelheim, Antwerp, Belgium; 3. Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands

Dr. Biondi-Zoccai has consulted for Boston Scientific, Cordis, and Mediolanum Cardio Research, and has received lecture fees from Bristol Myers Squibb; Dr. Agostoni has received lecture fees from Cordis. All other authors have no conflict of interest to declare.

KEYWORDS
Coronary artery disease; drug-eluting stent; evidence-based medicine; meta-analysis; systematic review

Abstract

The safety of drug-eluting stents (DES) in patients undergoing percutaneous coronary intervention has been questioned in several independent meta-analyses (i.e., systematic reviews of primary research studies employing statistical methods to provide pooled estimates) published or presented at the end of 2006. Other reviews and meta-analyses have followed in the beginning of 2007, albeit with unclear or conflicting results. This article provides a succinct perspective and critical appraisal of recently published meta-analyses focusing on DES safety, summarising key features and findings of each work, and recommending avenues for further research and practice.

* *Corresponding author: Interventional Cardiology, Division of Cardiology, University of Turin, S. Giovanni Battista-Molinette Hospital, Corso Bramante 88-90, 10126 Turin, Italy*
E-mail: isheiban@yahoo.com

Introduction

The occurrence of several duplicate meta-analyses focusing on the same clinical topic, and reaching sometimes frankly disparate conclusions, is not a surprise for researchers with a specific interest in systematic reviews or meta-analyses, as well as evidence-based medicine.[1] This issue has however gained much larger and clinical implications with the recent publication of a plethora of meta-analyses focusing on the long-term safety of intracoronary drug-eluting stents (DES). Interestingly, two meta-analyses presented at the 2006 World Congress of Cardiology,[2-3] both suggesting a potential late hazard with DES, have been followed by as many as other eight overlapping works published in peer-reviewed journals in less than seven months.[4-11]

We hereby provide a succinct and critical appraisal of recently published meta-analyses focusing on DES safety, summarising key features and findings of each work, and recommending avenues for further research.

Clinical and research context

Percutaneous coronary intervention (PCI) is a mainstay in the management of patients with coronary disease. Since its beginning as a balloon-only intervention, PCI was revolutionised by the introduction of bare-metal stents.[12] While addressing many of the drawbacks of balloon-only PCI (e.g., abrupt closure), standard stents are fraught by a significant risk of late failure due to neointimal hyperplasia and ensuing restenosis, especially in small vessels and long-lesions.[13] The most recent development of DES has enabled us to address the problem of neointimal hyperplasia, without sacrificing the mechanical properties of the metallic platform.

Despite several promising data limited to short term follow-up[14] or low risk patients,[15] since 2004 a number of reports were published suggesting a potential for late adverse events with DES.[16-17] Thus, it was only a matter of time before investigators with expertise in systematic reviewing processes and meta-analytic pooling would exploit the superior statistical power of these approaches to unmask the long-term increase in the risk of thrombotic events with DES.

Further contributions to this research topic have been recently provided by the consensus Academic Research Consortium (ARC) definitions of definite, probable, or possible stent thrombosis.[18] However, even in the ARC context there is still a risk of underestimating thrombotic events if adjudication is based only on angiography or pathology, and conversely, overestimating thrombosis rates if myocardial infarction and sudden cardiac death are considered as a proxy for stent thrombosis.

While there is little debate that DES increase in a statistically significant fashion the risk of protocol-defined stent thrombosis after dual antiplatelet discontinuation, the most important question is whether this risk is magnified as much as to become clinically relevant. We leave such a topic open to the discussion and informed decision of the reader, as this was indeed the main focus of all the meta-analyses recently published on DES, whose findings on the risk of stent thrombosis, as well as of other events, are summarised in Table 1.

Critical appraisal of available meta-analyses

Keeping in mind the guidelines from the Cochrane Collaboration,[19] the Quality of Reporting of Meta-analyses (QUOROM) statement,[20] and the Oxman-Guyatt index,[1] we recognised a number of limitations in the available DES meta-analyses. Indeed, a pivotal distinction should be made between meta-analyses based only on published and/or aggregate data, and thus limited in their ability to correct for incomplete or inaccurate data, and meta-analyses using data gathered at the patient or lesion level, in which all data sets from individual studies are pooled into a single data set, enhancing coherence and quality, and enabling sophisticated subgroup or multivariable analyses.[21] Conversely, the latter type of works is most often limited by a smaller number of studies, thus potentially increasing the risk of small study (e.g., publication) bias.

Appraisal of recent meta-analyses on DES thus showed, as is commonplace in meta-analytic practice, that individual patient data analyses[4,7-11] were often limited by incomplete study search and inclusion (thus increasing the risk of small study bias), despite being more internally valid than study level analyses,[2,5-6] thanks to thorough event adjudication, data checking and time-to-event analysis. Another work, despite being originally proposed as a meta-analysis, was recently published as a systematic review, including raw quantitative data, but failing to present conventionally pooled data.[3] The reasons for refraining from meta-analytic pooling in this case were not reported.

In addition, most works limited their adjudication of stent thrombosis to the protocol definition, which often proves different from study to study, and usually underestimates the real occurrence of this event. Only two of the meta-analyses systematically employed the recently developed ARC definitions of stent thrombosis, thus providing more informative data on its occurrence.[8,10] On the other hand, the ARC criteria now include as well thrombotic events occurring after repeated treatment for restenosis ("secondary stent thrombosis"). This may be appropriate if repeat intervention is performed with balloons or stents. Conversely, including events that occur after a well known pro-thrombotic therapy such as brachytherapy may be misleading.[8,10]

Finally, only one of the works was published by investigators without any evident financial or funding interest in DES,[2] as recommended by the Cochrane Collaboration and others.[19,22]

Synthesis and recommendations

First, we should remember that no clinical trial to date was adequately powered for the appraisal of stent thrombosis, and in no case was this event the primary end-point. Thus, all speculations have been based on secondary and/or post-hoc analyses. Nominally statistical significant findings ($p < 0.05$) were indeed found in some, but not all analyses, raising the issue of alpha error (the risk of false positive statistical tests due to the performance of many comparisons and sub-analyses). Similarly, no study to date was adequately powered (i.e., with a sample size sufficiently large to minimise beta error [the risk false negative findings]) to be able to confirm or disprove, in a precise and accurate fashion, whether DES are associated with an increased

Table 1. Main features and appraisal of recently published meta-analyses on the safety of drug-eluting stents (DES) in comparison to bare-metal stents (BMS). Despite the heterogeneous findings, most meta-analyses cautioned that DES are associated with an increased risk in protocol-defined stent thrombosis, and that sirolimus-eluting stents (SES) seem to be associated with increased mortality in diabetic patients. Conversely, thrombosis as defined by the Academic Research Consortium criteria (ARC), i.e., including secondary stent thrombosis, does not seem to be more common in DES than BMS.

Study	Trials	Patients	Major findings	Critical appraisal
Bavry et al (2006)[5]	14	6,675	DES are associated with an increase in late stent thrombosis after 6 months (p=0.014), even more evident after 1 year, with events occurring only in the DES group, with an effect larger in PES (p=0.025) than SES (p=0.33)	Pros: extensive search; inclusion of most eligible trials; increased late thrombotic risk also supported by different median times to thrombosis (p <0.05 for SES, PES, as well as both combined) Cons: only aggregate data pooled; no appraisal of study quality; no appraisal of stent thrombosis according to ARC definitions; non-significance of data on SES largely explained by low statistical power
Camenzind et al (2007)[3]	9	5,218	First-generation DES appear associated with an increased risk in late stent thrombosis or death/myocardial infarction	Pros: long-term follow-up; systematic contact with primary data sources (companies); comparison between data presented at conference proceedings, peer reviewed, and on file Cons: not formally a systematic review nor a meta-analysis; incomplete search and study inclusion;* limited data on providers of source data; only aggregate data pooled; no appraisal of stent thrombosis according to ARC definitions; concept that late loss and thrombosis risk are inversely associated is only theoretical and not evidence-based; 25 no confidence intervals or p values reported despite availability of quantitative data
Ellis et al (2007)[7]	4	3,445	PES are associated with increased risk of stent thrombosis >6 months (p=0.049)	Pros: individual patient data analysis; long-term follow-up Cons: incomplete search and study inclusion;* no appraisal of stent thrombosis according to ARC definitions; data limited to PES
Holmes et al (2006)[4]	4	1,748	SES are not significantly associated with increased risks of all cause death, cardiac death or stent thrombosis	Pros: individual patient data analysis; long-term follow-up Cons: incomplete search and study inclusion;* no appraisal of stent thrombosis according to ARC definitions; no separate appraisal of outcomes in diabetics; data limited to SES
Kastrati et al (2007)[11]	14	4,958	SES are overall safe and more effective than BMS in preventing TLR and MACE, but there is slight but significant increase in stent thrombosis after the first year (p=0.02)	Pros: extensive search; inclusion of most eligible trials; individual patient data analysis Cons: no appraisal of stent thrombosis according to ARC definitions; no separate appraisal of outcomes in diabetics; data limited to SES
Mauri et al (2007)[10]	8	4,545	DES are not significantly associated with increased risks of definite, probable or possible stent thrombosis as defined according to ARC	Pros: systematic re-adjudication of events according to ARC definitions; individual patient data analysis; long-term follow-up Cons: incomplete search and study inclusion;* 27% (9/33) of stent thromboses re-adjudicated according to ARC definitions in BMS group occurred indeed after brachytherapy
Moreno et al (2007)[6]	25	9,791	DES are associated with fewer myocardial infarctions than BMS at 6-12 months of follow-up (p=0.03)	Pros: extensive search; inclusion of most eligible trials Cons: mid-term follow-up only; only aggregate data pooled; no appraisal of study quality; among DES included also those eluting biolimus, everolimus, and tacrolimus; no adjustment for different duration of thienopyridine treatment
Nordmann et al (2006)[2]	17	8,221	DES are associated with an increased risk in non-cardiac death after 2-3 years, an effect largely driven by SES (p=0.014)	Pros: extensive search; inclusion of most eligible trials; lack of conflicts of interest Cons: only aggregate data pooled; no separate appraisal of outcomes in diabetics
Spaulding et al (2007)[8]	4	1,748	SES are associated with an increased risk of death in diabetics (p=0.008), while rates of death in non-diabetics, and of myocardial infarction and stent thrombosis overall are similar in SES and BMS	Pros: individual patient data analysis; long-term follow-up; separate analysis according to diabetic status; systematic re-adjudication of events according to ARC definitions; Cons: incomplete search and study inclusion;* 33% (5/15) of stent thromboses re-adjudicated according to ARC definitions in BMS group occurred indeed after brachytherapy; data limited to SES
Stone et al (2007)[9]	9	5,261	DES are associated with an increased risk of stent thrombosis >1 year (p<0.05), while rates of death or myocardial infarction are similar in DES and BMS	Pros: individual patient data analysis; long-term follow-up; Cons: incomplete search and study inclusion;* no appraisal of stent thrombosis according to ARC definitions; no separate appraisal of outcomes in diabetics

* this refers to search strategies or inclusion criteria inappropriately limiting the number of included studies (e.g., including only studies with follow-up >3 years [thus excluding those with follow-up <3 years] but willing, nonetheless, to provide precise quantitative synthesis for mid-term events; MACE=major adverse cardiovascular events; PES=paclitaxel-eluting stents; TLR=target lesion revascularisation

risk of thrombosis. This fact is also a clear reminder that statistical significance stemming from underpowered trials may not translate into clinically significant findings.

Most meta-analyses cautioned that DES are associated with an increased risk in protocol-defined stent thrombosis, and that sirolimus-eluting stents (SES) seem to be associated with increased mortality in diabetic patients. Conversely, ARC-defined thrombosis does not seem to be more common in DES than BMS. However, the ARC decision to include secondary stent thromboses (i.e., those occurring after repeat intervention, even brachytherapy), while correct according to the intention-to-treat principle, remains open to discussion and can be misleading in a setting where the primary goal is to understand the pathophysiological substrate of a potentially ominous event such as very late stent thrombosis.

Several practical actions can be recommended, and to this end we borrow recommendations from other colleagues to individualise patient management, including indications to percutaneous revascularisation vs surgery or medical therapy only, as well as indications toward a specific coronary device.[23]

In addition, and focusing more on the evident discrepancies or redundancies in the current DES literature, we would like to stress that in the future the following should be addressed:

- A more thorough comparison of per-protocol and ARC-defined stent thrombosis events, which includes reasons for discrepancies;
- A more thorough appraisal of the risks and benefits of DES (especially with SES) in diabetic vs non-diabetic patients;
- Strive for a unique, unanimous, collaborative, cumulative, prospectively planned and designed systematic review and individual patient data meta-analysis on DES similar to the one produced by the Antiplatelet Trialists' Collaboration.[24]

Acknowledgements

This work is part of an ongoing senior investigator program of the Centre for Overview, Meta-analysis, and Evidence-based medicine Training (COMET) based in Turin, Italy (http://www.comet.gs).

References

1. Biondi-Zoccai GG, Lotrionte M, Abbate A, Testa L, Remigi E, Burzotta F, Valgimigli M, Romagnoli E, Crea F, Agostoni P. Compliance with QUOROM and quality of reporting of overlapping meta-analyses on the role of acetylcysteine in the prevention of contrast associated nephropathy: case study. *BMJ* 2006;332:202-9.

2. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. *Eur Heart J* 2006;27:2784-814.

3. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation* 2007;115:1440-55.

4. Holmes DR Jr, Moses JW, Schofer J, Morice MC, Schampaert E, Leon MB. Cause of death with bare metal and sirolimus-eluting stents. *Eur Heart J* 2006;27:2815-22.

5. Bavry AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. *Am J Med* 2006;119:1056-61.

6. Moreno R, Fernandez C, Calvo L, Sanchez-Recalde A, Galeote G, Sanchez-Aquino R, Alfonso F, Macaya C, Lopez-Sendon JL. Meta-analysis comparing the effect of drug-eluting versus bare metal stents on risk of acute myocardial infarction during follow-up. *Am J Cardiol* 2007; 99:621-5.

7. Ellis SG, Colombo A, Grube E, Popma J, Koglin J, Dawkins KD, Stone GW. Incidence, timing, and correlates of stent thrombosis with the polymeric paclitaxel drug-eluting stent: a TAXUS II, IV, V, and VI meta-analysis of 3,445 patients followed for up to 3 years. *J Am Coll Cardiol* 2007;49:1043-51.

8. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007;356:989-97.

9. Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, Colombo A, Schampaert E, Grube E, Kirtane AJ, Cutlip DE, Fahy M, Pocock SJ, Mehran R, Leon MB. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med* 2007;356:998-1008.

10. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007;356:1020-9.

11. Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H, Menichelli M, Sabate M, Suttorp MJ, Baumgart D, Seyfarth M, Pfisterer ME, Schomig A. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med* 2007;356:1030-9.

12. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med* 1987;316:701-6.

13. Kasaoka S, Tobis JM, Akiyama T, Reimers B, Di Mario C, Wong ND, Colombo A. Angiographic and intravascular ultrasound predictors of in-stent restenosis. *J Am Coll Cardiol* 1998;32:1630-5.

14. Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoye A, Degertekin M, Tanabe K, Daemen J, Liu TK, McFadden E, Sianos G, Hofma SH, Smits PC, van der Giessen WJ, de Feyter PJ. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *Circulation* 2004;109:190-5.

15. Sousa JE, Costa MA, Abizaid A, Feres F, Seixas AC, Tanajura LF, Mattos LA, Falotico R, Jaeger J, Popma JJ, Serruys PW, Sousa AG. Four-year angiographic and intravascular ultrasound follow-up of patients treated with sirolimus-eluting stents. *Circulation* 2005;111:2326-9.

16. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004;364:1519-21.

17. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sanglorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;293:2126-30.

18. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344-51.

19. The Cochrane Collaboration Handbook for Systematic Reviews of Interventions. Available at: http://www.cochrane.org/resources/handbook/index.htm (last accessed on 30 May 2007).

20. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999;354:1896-900.

21. Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet* 1993;341:418-22.

22. Ligthart S, Viemmix F, Dendukuri N, Brophy JM. The cost-effectiveness of drug-eluting stents: a systematic review. *CMAJ* 2007;176:199-205.

23. Hodgson JM, Stone GW, Lincoff AM, Klein L, Walpole H, Bottner R, Weiner BH, Leon MB, Feldman T, Babb J, Dehmer GJ; Society for Cardiovascular Angiography and Interventions. Late stent thrombosis: considerations and practical advice for the use of drug-eluting stents: a report from the Society for Cardiovascular Angiography and Interventions Drug-eluting Stent Task Force. *Catheter Cardiovasc Interv* 2007;69:327-33.

24. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86.

25. Agostoni P, Sanglorgi GM, Biondi-Zoccai GG. Treatment of restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med* 2007;356:1071-2.

CHAPTER 16

THE TANDEMHEART®, PERCUTANEOUS TRANSSEPTAL LEFT VENTRICULAR ASSIST DEVICE: A SAFEGUARD IN HIGH-RISK PERCUTANEOUS CORONARY INTERVENTIONS. THE SIX-YEAR ROTTERDAM EXPERIENCE

EuroIntervention

The TandemHeart®, percutaneous transseptal left ventricular assist device: a safeguard in high-risk percutaneous coronary interventions. The six-year Rotterdam experience

Pascal Vranckx[1,3], MD; Emanuele Meliga [2,4], MD; Peter PT De Jaegere[2], MD PhD; Martin Van den Ent[2], MD PhD; Evelyn S Regar[2], MD PhD; Patrick W Serruys[2]*, MD PhD FESC FACC

1. Department of Cardiac Intensive Care & Interventional Cardiology, Virga Jesseziekenhuis, Hasselt, Belgium; 2. Department of Interventional Cardiology, Thoraxcenter, Erasmus Medical Centre, Rotterdam, The Netherlands; 3. Cardialysis B.V., Clinical Research Organisation & Core Laboratories, Rotterdam, The Netherlands; 4. Department of Interventional Cardiology, S. Giovanni Battista Hospital, University of Turin, Turin, Italy

None of the authors have a conflict of interest to declare.

KEYWORDS
Heart-assist device, angioplasty, TandemHeart®

Abstract

Aims: Percutaneous coronary interventions (PCI) in high-risk cardiac patients are preferentially referred to specialised myocardial intervention centres (MIC). Included in this group are patients with a haemodynamic collapse or high likelihood of haemodynamic collapse, either during balloon inflation or with acute vessel closure. The TandemHeart®, a percutaneous transseptal left ventricular assist (PTVA®) that can be introduced using standard catheterisation laboratory techniques, offers interesting perspectives to reduce procedural risks.

Methods and results: Between September 2000 to July 2006, The TandemHeart®, supported the circulation of 23 patients (age: range 46-74, mean 59) admitted to our centre for high risk, either emergency or elective, PCI. Successful implantation was achieved in 100% of patients. The mean time for implementation of circulatory support was 35 minutes (range 16-62). The index PCI was successful in all patients except two. A pump flow up to 4L/min was achieved with significant reduction of left ventricular filling pressures, pulmonary capillary wedge pressure and with significant increase of systemic arterial pressures. Duration of support ranged from 1-222 hours (mean 31±49.8 hours). Five patients died with the TandemHeart® in place, four of whom were in irreversible cardiogenic shock at admission. Mild to moderate access site bleeding was seen in 27% of patients. One patient experienced a loge syndrome of the leg. Core temperature (Ct) decreased to <36.5°C in six patients, profound hypothermia (Ct < 35°C) was observed in two patients. There was no technical device failure.

Conclusions: The TandemHeart® - PTVA® provides effective, total left ventricular support in very high risk PCI settings. The rate of device related cardiac and vascular complications was acceptable.

* *Corresponding author: Dpt. of Interventional Cardiology, Thoraxcenter, Ba583a, Erasmus Medical Centre, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands*
E-mail: p.w.j.c.serruys@erasmusmc.nl

Introduction

With increasing operator experience, refinement in technology and adjunctive pharmacological treatment, percutaneous coronary intervention (PCI) is now considered the treatment of choice for many high-risk subgroups in which PCI was previously contra-indicated. PCI may even be a valuable option for those patients where coronary bypass grafting (CABG) is clinically contra-indicated[1-3]. Many of these procedures are elective.

In general the benefits of a specific (percutaneous) procedure should be weighed against the risks involved; taking into account alternative treatment strategies, the interventional and intensive care team experience[4] and taking in consideration the individual patient risk scores, that may aid the operator in selecting or avoiding adjunctive pharmacotherapy or specific devices[5-9].

Patients in whom it is considered that PCI poses a significantly high risk include these with high likelihood of haemodynamic collapse, either during balloon inflation or with acute vessel closure[4]. In general, these are the patients in whom a large amount of the viable myocardium is supplied directly or indirectly by the affected artery. The development of a percutaneous ventricular assist device (VAD) that could be easily and quickly inserted prophylactically or in case of an haemodynamic collapse proves invaluable in this setting.

The TandemHeart®, a percutaneous transseptal left ventricular assist device (PTVA®) system (CardiacAssist Inc., Pittsburgh, PA, USA), has been demonstrated to effectively reverse cardiogenic shock after myocardial infarction[11] and to play an important role for bridging to another definitive therapy[12]. This system allows for rapid implementation of circulatory support using standard interventional techniques in the catheterisation laboratory and is designed to deliver up to 4.5 litres of blood flow per minute. In this report, we will report on a single centre six year clinical experience with the TandemHeart® in high risk PCI procedures.

Methods

Patients selection

Since 2000, the Thoraxcenter, Erasmus University Medical Centre, Rotterdam, The Netherlands started a program evaluating percutaneous left ventricular assist devices (LVAD) during high risk PCI. Between September 2000 to July 2006, twenty-three patients admitted to our centre for acute coronary syndromes (ACS)/ ST segment elevation myocardial infarction (STEMI) or for elective PCI, were treated with TandemHeart®.

In non-elective patients, the indication for TandemHeart® support was based on already established haemodynamic instability before the index PCI procedure, defined as typically with low cardiac output (cardiac index < 2.2 L/min/m^2), peripheral signs of tissue hypoperfusion (decreased urine output and/or cold extremities), systemic hypotension (systolic blood pressure < 100 mmHg) despite vasopressor therapy and in the presence of appropriate left ventricular filling pressures (pulmonary capillary wedge pressure, PCWP ≥ 15 mmHg). In case of presence of an intra aortic balloon pump (IABP) haemodynamic measurements were done with the IABP paused for 60 seconds.

In patients who underwent elective PCI, circulatory assist was indicated in procedures which had a presumed high risk of ischaemic/haemodynamic complications, based on the presence of severely depressed left ventricular (LV) function and planned treatment of ≥ one complex lesions in vessels supplying a large amount of myocardium. CABG was not considered a treatment option in any of these patients. Major exclusion criteria were predominant right ventricular failure requiring right ventricular support, severe aortic insufficiency, severe sepsis and anoxic brain damage.

System description

The TandemHeart® PTVA® (Figure 1-2) incorporates arterial perfusion cannula configurations ranging from 9 to 17 Fr, an unique 21 Fr venous transseptal cannula, and a centrifugal blood pump. Oxygenated blood from the patient's left atrium is supplied to the pump by the trans-septal cannula and than returned to the patient's systemic arterial circulation. The centrifugal pump contains a single moving part (rotor/impeller) that is suspended by a thin lubricating film of fluid to reduce heat and friction, thereby reducing the risk of thrombus formation. The pump connects to a microprocessor-based controller that displays PTVA speed and flow. These parameters are controlled by adjustment of a single knob. The controller also provides automatic system monitoring and alarms indicating conditions that require action. The system is designed to deliver up to 4.5-5 litres (L) of blood flow per minute, depending on the size of the arterial cannulation and the filling conditions of the left atrium, while operating at a relatively low speed (7500 revolutions per minute, RPM).

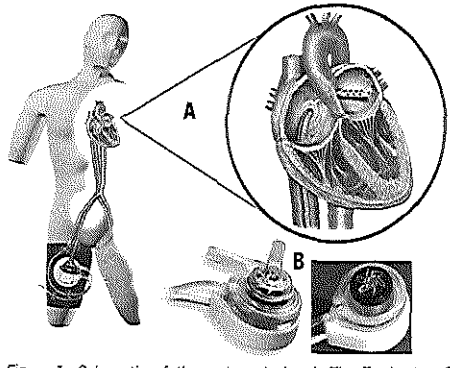


Figure 1. Schematic of the system deployed. The Tandemheart® removes oxygenated blood from the left atrium via a 21 Fr transseptal cannula that is advanced from the femoral vein trough the inter-atrial septum into the left atrium (A). The oxygenated blood is returned into the arterial vascular system via a 15 up to 17 Fr arterial cannula by means of a centrifugal pump (B). The centrifugal pump contains a single moving part (rotor/impeller) that is suspended by magnetic force on a thin lubricating film of fluid to reduce heat and friction, thereby reducing the risk of thrombus formation.

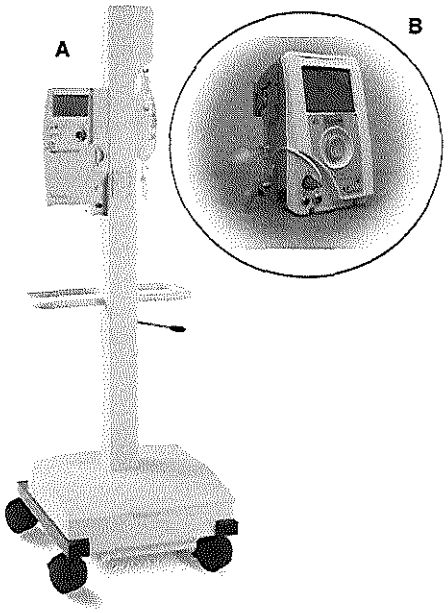


Figure 2. Microprocessor-based controller used in this series (A) displaying PTVA speed and flow. These parameters are controlled by adjustment of a single knob. The controller includes extensive self-diagnostic and alarm features to ensure patient support without the need for constant operator surveillance. Panel (B) shows the recently introduced Escort Controller. This light (21 pound or 9.53 kg) weight controller can be mounted at the patient's bedside and includes an easy-load infusion system. The latter allows the lubrication fluid infusion line to be installed in seconds.

Insertion technique

A standard transseptal puncture technique, using an Inoue guidewire, was used to gain access into the left atrium from the right femoral vein. Transseptal puncture was carried out by an experienced operator only. The inter-atrial septum was dilated with an 2-stage 14/21 Fr dilator and the venous inflow cannula was inserted (proper positioning in the left atrium was checked by either angiography and/or transesophageal echocardiography). One 15 Fr or 17 Fr perfusion catheter (Bio-medicus cannula, Medtronic, Minneapolis, MN, USA) was inserted into the femoral artery and advanced to the common iliac artery. An ileac angiography was performed before the placement of the perfusion catheter to delineate the arterial anatomy and size and to disclose eventual luminal obstructions. In three patients a dual femoral approach with Y connection was used for arterial access. Both arterial and venous cannula were fixed to the skin with multiple sutures in order to secure their position. The pump was placed on the upper leg of the patient. After checking the central venous pressure, priming and cautious de-airing of the entire system, the arterial and venous cannulas sets were connected to the pump by a heparin-coated tygon tubing (up to 30 cm length) and the pump was activated to its maximum rotation speed. Output pump flow was measured by an external electromagnetic flow meter (HT 311, transonic).

Device weaning and removal

A predefined weaning protocol was initiated at the moment vasoactive drugs were reduced to a stable minimal level (dobutamine up to 4 µg/kg/min., norepinephrine up to 0.1 4 µg/kg/min.) provided stable haemodynamic parameters (mixed venous or central venous saturation > 65%). A stepwise reduction of pump assist was performed, by reducing pump speed from 7500 to 3500 RPM (steps of 500-1,000 mL/min), adapted to the medical condition of each patient individually. The final removal decision was based on medical judgement. A weaning period up to six months was respected for most patients. The pump was not stopped until immediately before removal. No specific instructions on access site closure were issued.

Concomitant treatment

The index coronary intervention was performed after TandemHeart® implantation and functioning. Arterial access was obtained via the contra-lateral femoral artery and the interventional strategy was left to the operator, according to standard techniques. Standard intensive care was provided to each patient. Patient sedation and intubation was considered for clinical and/or comfort reasons. A balloon tipped pulmonary artery (PA) catheter was placed via the contra lateral femoral vein for haemodynamic monitoring purposes if clinically indicated. Cardiac output determinations were made using standard thermodilution techniques.

During the index procedure, a constant flow (10 ml/h) of heparinised infusate is maintained providing a localised concentration of heparin in the interior of the pump in order to obtain localised anti-coagulation thereby minimising systemic heparinisation, the risk of bleeding and thrombus formation. Additional boluses of heparin were administered peripherally to maintain the activated coagulation time to approximately 200 seconds during routine support (400 seconds during insertion) or an activated partial thromboplastin time of between 65 and 80 seconds.

Predefined safety endpoints and time periods

The following predefined clinical events related to the use of the TandemHeart® were assessed in each patient: any minor or major TIMI bleeding[9], laceration of the insertion vessel/limb ischaemia, device related thromboembolic events, infective complications, residual atrial septum defect after device removal, device malfunction or failure.

The insertion time was defined as the time from providing of the Brockenbrough needle to the 'full' heparinisation following connection of the femoral cannula to the pump. The duration of support was defined as the time from 'full' heparinisation at time of connection to the pump till the removal of the femoral cannula.

Statistical analysis

Variables with normal distribution were analysed using parametric tests while variables with a non-normal distribution were analysed with non-parametric tests. Continuous variables are expressed as mean ±SD or median ±SD and differences are compared using

Student t test or Mann Whitney test. Categorical variables are expressed as counts and percentages. Differences were assessed by Fisher exact test or chi-square test, as appropriate. All analyses were performed using SPSS version 12 statistical software (SPSS Inc., Chicago, IL, USA). A two-tailed p value < 0.05 was considered significant for hypothesis testing.

Results

Baseline characteristics

Baseline clinical and procedural characteristics are listed in Table 1. Mean age was 59 ± 9.4 years, 19 patients (83%) were men. The ejection fraction was <30% in 16 patients (70%). Fifteen patients (65%) suffered a three vessel disease, six of whom with left main involvement. The indications for TandemHeart® support were elective/high risk PCI in 15 patients and non-elective (emergency) in eight patients with ACS and acute heart failure. Eight patients experienced an evolving (< 36 hours) myocardial infarction, five of which were complicated by acute heart failure/cardiogenic shock (CS). Eight patients needed intubation and mechanical ventilation as part of their medical treatment and 11 were on inotropic support at the start of the implant procedure. Standard EuroScore in our patients ranged between 2 and 14 (mean 6.5) providing a surgical risk of mortality between 1.5% and 46.6% (mean: 11.3±11.6%). Very high risk patients (EuroScore > 9) were nine[13].

Haemodynamic effects

The TandemHeart® showed good performance, achieving flow rates up to 4.0 L/min. Mean systemic arterial pressure was 74.8±18 mmHg at baseline and 85.6±19 mmHg after pump functioning (p= 0.023).

Table 1. Baseline characteristics; n (%)

Age (mean±SD)		59±9.4
Sex	M	19 (82.6)
	F	4 (17.4)
Previous MI		11 (47.8)
Previous CABG		4 (17.4)
Clinical presentation	STEMI&CS	5 (21.7)
	STEMI	3 (13)
	NSTEMI	1 (4.3)
	UA	5 (21.7)
	Angina/dyspnea	8 (34.7)
	Scheduled PCI	1 (4.3)
CAD extension (23 pts)	1VD	3 (13)
	2VD	5 (21.7)
	3VD	9 (39.1)
	3VD + LM	6 (26)
EF	<20%	11 (47.8)
	20-30%	5 (21.7)
	30-50%	3 (13)
	>50%	4 (17.4)
Indication for PTVA	elective	15 (65.2)
	emergency	8 (34.7)
Intubation		8 (34.7)
Inotropic support		11 (47.8)
EuroScore (mean±SD)		6.5±3.4
	HRP (>6)	3 (13)
	VHRP (>9)	9 (39.1)

Pulmonary wedge pressure was 16.8±5.6 mmHg at baseline and 13.6±6 after pump functioning (P= 0.002). The pulse pressure was reduced on support from 39.7±17.7 to 31.5±17 (p<0.001) (Table 2). In two patients the initial period after implantation of the TandemHeart® was characterised by a complete non- pulsatile arterial blood pressure (pulse pressure < 7 mmHg). In one patient with the recovery of the heart function < 24 hours after implantation, increasing pulse pressures became evident. Modulation of pulsatility with low amplitude to the non-pulsatile blood flow produced by the PTVA could be achieved by varying pump flow. One patient did not show recovery of pulsatile blood flow and he died with the TandemHeart® *in situ*.

Table 2. Hemodynamic effects of PTVA.

	Baseline	PTVA	P value
MSBP (mean±SD)	74.8±18	85.6±19	0,023
Pulse P (mean±SD)	39.7±17.7	31.5±17	0,001
PCWP (mean±SD)	16.8±5.6	13.6±6	0,002

A pulmonary artery catheter was inserted in 20 out of 23 patients. The hemodynamic measurements reported were immediately before Tandem Heart® insertion and at the end of the PCI procedure (before the patient was transferred to the cardiac intensive care department)

Procedural and clinical outcomes

Procedural and clinical outcomes are summarised in Table 3. Index-PCI procedural success was achieved in 42 lesions (96%). A total of 44 lesions were treated (one up to four lesions per patient), all including stent implantation (mean stent per patient rate: 2.3). The mean time for insertion of the TandemHeart® was 34±12 minutes (range 16-62), the procedural success was 100%. The circulatory assist period ranged from 1h to 222h, mean 31±49.8h One patient with a severe femoral artery stenosis needed PTA and stenting of the iliac artery vessel prior to cannulation.

Seventeen patients were successfully weaned from the TandemHeart®, in-hospital death occurred in six patients. In total five patients died with the device *in situ*, four of which were considered in irreversible CS at admission. Another patient admitted for CS was initially stabilised after 222 hours on TandemHeart®

Table 3.

PCI Results; n (%)		
PCI success rate		96%
Number of treated lesions		44
Stent per patient		2,3
PTVA Insertion success rate		100%
PTVA Insertion Time (mean±SD)		34±12
Assist period, hours (range/mean±SD)		1-222/31±49.8
Death	In hospital	6 (26)
	with PTVA in place	5* (22)
	at 6 months FU	9 (39)
	at 12 months FU	10 (43)
	at 2 years	11 (47)
	at 5 years	11 (47)

* 4/5 patients suffered cardiogenic shock

support. However, this patient developed abrupt circulatory failure after removal of the pump and died a few hours later. No further invasive treatment was possible due to the abrupt worsening of his clinical condition. During the follow-up period, three patients were lost and one patient died due to progressive heart failure <30 days. An uneventful six months follow-up was observed in 13 patients.

Complications

Potential complications related with the use of TandemHeart® are summarised in Table 4. In this series of patients, no procedural complications during device insertion were noted and no cardiac tamponade, thromboembolic events nor device failure occurred. In two elective cases (8.7%) the weaning needed to be postponed due to the occurrence of profound hypothermia (core temperature 32.7 °C and 34.2 °C) and the need for active re-warming. Minor to mild access site bleeding complications occurred in 26% of patients (n=6), none required specific treatment. Lower limb ischaemia complicated by a loge syndrome occurred in one patient with pre-existing severe peripheral vascular disease. This patient needed a fasciotomy. Dislocation of the venous cannula occurred in one patient and required pump removal.

Most pumps were surgically removed in the operation theatre (n=12, 52%). A closure device (Prostar) failed to close completely the puncture site in two out of three attempts. A local compression device (Femostop, Radi) was used successfully in these patients as well as in three others without any complication.

Table 4. Potential complications of PTVA; n(%)

Puncture of aortic root, coronary sinus, posterior free wall	0 (0)
TandemHeart pVAD system failure	0 (0)
Thromboembolism	0 (0)
Neurologic dysfunction	0 (0)
Hemolysis	0 (0)
Cardiac tamponade	0 (0)
Deep venous thrombosis	0 (0)
Arrhythmias	0 (0)
Systemic hypothermia (35-36.5)	4 (17.4)
Profound hypotermia (<35)	2 (8.7)
Bleeding	6 (26)
Cannulation site infection	0
Cannula dislogment	0
Distal leg ischaemia	1 (4.3)
Total no. of events	13

Table 5. Exclusion criteria for this study were:

- Participation in another trial with an investigational drug/ device during the last 60 days
- Concomitant disease that interferes with the prognosis.
- Contra indications to standard drugs for coronary intervention and coronary heart disease.
- Coagulopathy-chronic anticoagulant therapy / uncontrolled active bleeding.
- CNS damage resulting in fixed dilated pupils not related to pharmacologics.
- Severe aortic/mitral valve stenosis, significant aortic valve insufficiency.
- Rupture of the ventricular wall
- Right heart failure, defined as the need of a right ventricular assist device.
- Severe peripheral vascular disease (e.g. aorto-iliac occlusive disease).
- Stroke of haemorrhagic or unknown origin
- Non-haemorrhagic stroke, that took place within the past 30 days
- A transient ischaemic attack, that took place within the past 30 days.

Discussion

PCI in high-risk coronary patients with (potential) haemodynamic compromise is challenging and may be considered a special dimension of MIC[14]. Active circulatory support using VAD constitutes a valuable safeguard to reduce potential fatal intervention-related complications in this setting and is nowadays considered part of the current therapeutic armamentarium.

IABP is currently the most widespread mechanical device used to support and to improve coronary perfusion in patients with acute heart failure. IABP implantation is easy and its use is safe and associated with a low incidence of serious complications. IABP may provide a lot of diastolic augmentation of coronary flow in patients in shock, however only limited forward output augmentation (up to about 0.5 L/min). This level of support has been shown to be scarcely able to improve clinical outcomes in the setting of complete hemodynamic collapse[15].

Active circulatory support using VAD combines the beneficial effects of the myocardial unloading and an increase in tissue perfusion pressure. Theoretically, this technique should also allow very early decompression ("unloading") of the left ventricle in massive myocardial infarction, thus enhancing the chances of recovery of the jeopardised ischemic non-infarcted areas[16]. In animal models, LV unloading prior to revascularisation of the infarcted artery led to significant myocardial salvage in comparison to the implementation of unloading after reperfusion[17]. A trial testing this concept, including one patient reported in this series, was stopped early due to poor recruitment. However, the concept could nicely be illustrated by echo contrast imaging in one of our patients (Figure 3). Our data confirmed that TandemHeart® support was associated with significant decreases in left ventricular filling pressures, mean systolic blood pressure and arterial pressures. The blood flow, up to 4.5 L/min, provided by the device may be sufficient to both optimally unload the LV and to prevent and even reverse organ dysfunction in cardiogenic shock patients[11,18].

Patient selection is the single most crucial factor in determining a successful outcome in patients who receive temporary mechanical circulatory support. Rapid diagnosis and treatment are essential but are often based on limited information. The patient's history and overall clinical setting should be considered in the decision process to initiate circulatory support. A pulmonary-catheter was used in the majority of the patients as adequate left ventricular filling conditions are essential for proper functioning of (preload to) the device. Haemodynamic data, including mixed (or central) venous oxygen saturation, may help to guide the overall patient selection, the

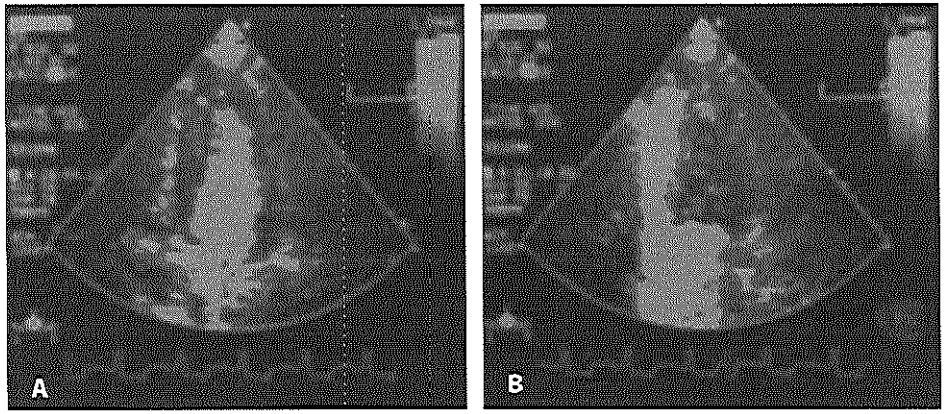


Figure 3. Echocardiographic contrast perfusion images in a patient on Tandemheart(r) circulatory support. Panel A: low circulatory support (high wall tension, poor myocardial perfusion, contrast remains in the ventricle cavity). Panel B: Full circulatory support with effective unloading of the left ventricle (low wall tension, good myocardial perfusion).

management and potential weaning decisions. In our series five patients died while on TandemHeart® support, four were in profound CS at the time of treatment initiation. Patients beyond the 'irreversible edge' of CS prove bad candidates for this technique in this and other series[11]. Of interest, only three out of the successfully weaned patients (n=17) deceased during the FU period, suggesting this device may have a tangible impact on the long-term survival as well.

The TandemHeart® can be used prophylactically and in bail-out situations. In experienced hands cardiovascular support can be implemented in less than 35 minutes. The most important drawback of the technique may be the difficulty of cannula insertion. Substantial atherosclerotic changes in the iliac artery and the consequent peripheral vascular disease are most common in the group of coronary patients who most benefit from the effects of the pump. In this series, a total number of 13 device-related in-hospital adverse events rate were observed, 0.6 events per patient. Many of them were access site complications. One patient developed a loge syndrome requesting a fasciotomy, but no other iatrogenic arterial insufficiency was noticed. Mild to moderate groin bleeding was encountered in six out of 23 patients (27%), none needing a specific treatment. Most pumps were surgically removed in the operation theatre in order to allow optimal local haemostasis and proper inspection of the cannulation site. A local compression or closure device may provide a valuable alternative given a clean puncture technique. Access site complications may be minimised by prior iliac angiography and by implementing an ultrasound guided puncture technique of the (common) femoral artery[13]. When necessary, the use of distal perfusion and antegrade cannulation of the superficial femoral artery may obviate peripheral vascular complications as well.

As opposed to other modalities of percutaneous cardiopulmonary support (CPS) used in this indication[19,20], the TandemHeart® system keeps the patient's lungs as its own ventilator and may be used to support patients for a longer period of time without major haematological or pulmonary complications (up to 10 days in our series). No thrombi formation was noticed either during the support or after the removal of the device and no thromboembolic event occurred. Evidence of clinical relevant haemolysis, which was a particular concern, was looked for but absent in our series (data not shown). Also this observation is in line with the Leipzig series[11].

Systemic hypothermia (<36,5°C) was observed in 25% of patients (n=6) but the temperature decreased below 35°C only in two cases. Contact of the system circuit with room temperature may have contributed to a cooling effect on the blood flowing through the pump. Other factors that may have contributed to heat loss are the use of general anaesthetic agents and neuromuscular blockers leading to vasodilatation and the loss of muscular tonus. Correcting measures may be straightforwardly introduced to avoid or rapidly detect this complication in the future.

Conclusion

Our results create optimism for more widespread introduction of the TandemHeart® in the MIC setting. The concept of closed chest left heart bypass, with left atrial to femoral artery bypass, constitutes a relatively safe and reliable safeguard in high risk PCI and acute heart failure. TandemHeart® PTLA® can be rapidly and percutaneously implanted in the catheterisation suite using standard interventional techniques in both a prophylactic or emergency settings. The TandemHeart® provides more haemodynamic support than the IABP and is effective in stabilising haemodynamics. Access site complications remain the Achilles' heel of this technique.

References

1. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med.* 2001; 344: 1117-1124.

2. Serruys PW, Ong AT, van Herwerden LA, Sousa JE, Jatene AD, Bonnier JJ, Schonberger JP, Buller N, Bonser R, Disco C, Backx B, Firth B, Unger F. Five year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol.* 2005; 46: 575-581

3. Topol EJ, Serruys PW. Frontiers in Interventional cardiology. *Circulation* 1998;98:1802-1820.

4. de Feyter PJ, McFadden E. Risk score for percutaneous coronary intervention: forewarned is forearmed. *J Am Coll Cardiol* 2003;42(10):1729-30.

5. Singh M, Lennon RJ, Holmes DR, Jr., Bell MR, Rihal CS. Correlates of procedural complications and a simple integer risk score for percutaneous coronary intervention. *J Am Coll Cardiol* 2002;40(3):387-93.

6. Singh M, Rihal CS, Selzer F, Kip KE, Detre K, Holmes DR. Validation of Mayo Clinic risk adjustment model for in-hospital complications after percutaneous coronary interventions, using the National Heart, Lung, and Blood Institute dynamic registry. *J Am Coll Cardiol* 2003;42(10):1722-8.

7. Vanagas G, Kinduris S, Buivydaite K. Assessment of validity for EuroSCORE risk stratification system. *Scand Cardiovasc J* 2005;39(1-2):67-70.

8. Berman M, Stamler A, Sahar G, Georghiou GP, Sharoni E, Brauner R, Medalion B, Vidne BA, Kogan A. Validation of the 2000 Bernstein-Parsonnet score versus the EuroSCORE as a prognostic tool in cardiac surgery. *Ann Thorac Surg* 2006;81(2):537-40.

9. Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, Bell WR, Knatterud G, Robertson TL, Terrin ML. Thrombolysis in Myocardial Infarction (TIMI) Trial: phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol.* 1988; 11: 1-11.

10. Kawachi Y, Nakashima A, Toshima Y, Arinaga K, Kawano H. Risk stratification analysis of operative mortality in heart and thoracic aorta surgery: comparison between Parsonnet and EuroSCORE additive model. *Eur J Cardiothorac Surg* 2001;20(5):961-6.

11. Thiele H, Lauer B, Hambrecht R, Boudriot E, Cohen HA, Schuler G. Reversal of cardiogenic shock by percutaneous left atrial-to-femoral arterial bypass assistance. *Circulation* 2001;104(24):2917-22.

12. Burkhoff D, O'Neill W, Bruckhorst C, Letts D, Lasorda D, Cohen HA. Feasibility study of the use of the TandemHeart percutaneous ventricular assist device for treatment of cardiogenic shock. *Catheter Cardiovasc Interv* 2006;68(2):211-7.

13. Toumpoulis IK, Anagnostopoulos CE. Can EuroSCORE accurately predict long-term outcome after cardiac surgery? *Nat Clin Pract Cardiovasc Med* 2005;2(12):620-1.

14. Vaina S, Stefanadis C. Treatment of multi-vessel coronary artery disease. What is the optimal revascularisation approach? What do we know, what will we learn? *Hellenic J Cardiol* 2007;48(1):1-4.

15. DeWood MA, Notske RN, Hensley GR, et al. Intraaortic balloon counterpulsation with and without reperfusion for myocardial infarction shock. *Circulation* 1980;61:1105-1112.

16. Laks H, Rosenbranz ER, Buckberg GD. Surgical treatment of cardiogenic shock after myocardial infarction. *Circulation* 1986; 74 (suppl III): 15-22.

17. Meyns B, Stolinski J, Leunens V, et al. Left ventricular support by catheter-mounted axial flow pump reduces infarct size. *J Am Coll Cardiol* 2003;41:1087-1095.

18. Thiele H, Sick P, Boudriot E, Diederich KW, Hambrecht R, Niebauer J, Schuler G. Randomized comparison of intra-aortic balloon support with a percutaneous left ventricular assist device in patients with revascularized acute myocardial infarction complicated by cardiogenic shock. *Eur Heart J* 2005;26(13):1276-83.

19. Shawl FA, Domanski MJ, Wish MH, Davis M. Percutaneous cardiopulmonary bypass support in the catheterization laboratory: technique and complications. *Am Heart J* 1990;120(1):195-203.

20. Vogel RA, Shawl F, Tommaso C, O'Neill W, Overlie P, O'Toole J, Vandormael M, Topol E, Tabari KK, Vogel J and others. Initial report of the National Registry of Elective Cardiopulmonary Bypass Supported Coronary Angioplasty. *J Am Coll Cardiol* 1990;15(1):23-9.

PART 4

HYPERTROPHIC CARDIOMYOPATHY

CHAPTER 17

ACUTE EFFECTS OF ALCOHOL SEPTAL ABLATION ON SYSTOLIC AND DIASTOLIC LEFT VENTRICULAR FUNCTION IN PATIENTS WITH HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

Original article

Acute effects of alcohol septal ablation on systolic and diastolic left ventricular function in patients with hypertrophic obstructive cardiomyopathy

P Steendijk,[1] E Meliga,[2,3] M Valgimigli,[2] F J Ten Cate,[2] P W Serruys[2]

[1] Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; [2] Department of Interventional Cardiology, Thoraxcentar, Erasmus Medical Center, Rotterdam, The Netherlands; [3] Department of Interventional Cardiology, S Giovanni Battista Hospital, University of Turin, Turin, Italy

Correspondence to: Dr Paul Steendijk, Leiden University Medical Center, Department of Cardiology, PO Box 9600, 2300 RC Leiden, The Netherlands; p.steendijk@lumc.nl

Accepted 11 March 2008
Published Online First 1 May 2008

ABSTRACT

Objective: Hypertrophic obstructive cardiomyopathy (HOCM) often leads to heart failure, severe symptoms and death. Percutaneous transluminal septal myocardial ablation (PTSMA) by alcohol injection efficiently reduces left ventricular (LV) outflow tract pressure gradient and improves symptoms. We determined acute changes in haemodynamics and systolic and diastolic LV function after PTSMA.

Methods: In 17 consecutive patients with symptomatic HOCM referred for PTSMA, the target vessel was determined by myocardial contrast transthoracic echocardiography. An over-the-wire balloon was inflated in the target vessel and multiple 0.5-ml alcohol injections were performed. LV systolic and diastolic function was assessed by online pressure-volume loops obtained by conductance catheter at baseline and acutely after the procedure.

Results: In all patients except two, a single septal branch was treated using a total of 2.0 (0.5) ml ethanol per patient. The rest and post-extrasystolic gradient were significantly decreased after PTSMA (79 (38) to 14 (16) mm Hg and 130 (50) to 34 (33) mm Hg, respectively, both $p<0.001$). Ejection fraction decreased (78% (9%) to 67% (13%), $p<0.001$). Cardiac output, heart rate and stroke work were unchanged, but systolic and diastolic volume increased. End-systolic and end-diastolic pressure significantly decreased (166 (27) to 129 (26) mm Hg, $p<0.001$ and 25 (6) to 21 (7) mm Hg, $p = 0.049$, respectively). Significant rightward shift ($p<0.001$) and decreased slope ($p = 0.041$) of the end-systolic pressure-volume relation indicated reduced contractility, whereas diastolic stiffness, $-dP/dt_{MIN}$, and tau were significantly improved after the procedure.

Conclusions: PTSMA acutely reduced systolic function but promptly improved diastolic function with maintained cardiac output and stroke work. Improved diastolic function and increased end-diastolic volume compensated for the systolic loss and resulted in maintained haemodynamics.

Hypertrophic obstructive cardiomyopathy (HOCM) is a genetic cardiac disease which is characterised by interventricular septum hypertrophy, a narrowed left ventricular outflow tract (LVOT), mitral regurgitation and mitral valve systolic anterior motion (SAM) resulting in LVOT obstruction.[1] Patients with HOCM are at high risk of dying or developing severe symptoms, and LVOT obstruction has been shown to be an independent predictor of development of heart failure symptoms and death.[2 3] In patients who remain symptomatic despite optimal medical therapy, surgical removal of a small amount of muscle from the basal interventricular septum has been shown to be an effective therapy.[4] Recently, percutaneous transluminal septal myocardial ablation (PTSMA) was introduced as an attractive alternative procedure.[5–10] PTSMA induces myocardial infarction by selective injection of alcohol into one or more septal branches of the left anterior descending coronary artery aiming at contractile dysfunction and thinning of the septum to reduce the LVOT pressure gradient.[11] Significant and sustained decreases in LV outflow tract pressure gradients have been reported in several studies after PTSMA at long-term follow-up,[6 7 12] although a recent study indicated less favourable effects in young patients with high baseline resting gradients.[10] The role of PTSMA in reducing mitral regurgitation and SAM is still uncertain.[5] The aim of this study was to establish the acute changes in systolic and diastolic left ventricular function after PTSMA in order to better understand the complex series of events that follow the procedure and that result in a new haemodynamic status.

METHODS

Patient population

The study population consisted of 17 consecutive patients with symptomatic HOCM despite optimal medical treatment who were referred for PTSMA at the Thoraxcenter. The HOCM diagnosis was based on typical clinical, echocardiographic and angiocardiographic findings. The inclusion criteria were New York Heart Association (NYHA) classification class II–IV, associated with any sign of obstructive LVOT: resting systolic gradient greater than 50 mm Hg or septal thickness greater than 15 mm, or a less than 7-mm LVOT diameter or SAM of anterior mitral leaflet. The study group included two patients with confirmed familial HOCM and four patients in whom HOCM was presumably related to previous hypertension. In the remaining patients the origin was unknown. The study was approved by the internal review board of the Erasmus Medical Centre and all patients provided informed consent before participation.

PTSMA procedure

A 6F transfemoral temporary pacemaker was positioned in the right ventricle. Baseline haemodynamic data, including LVOT gradient at rest and at provocation with the Valsalva manoeuvre, were measured via two retrograde 6F catheters introduced percutaneously via the femoral artery and

placed one in the left ventricle and one in the ascending aorta. Intraprocedural myocardial contrast transthoracic echocardiography (TTE) was performed to determine the target vessel. The vessel was then selectively probed with a 0.014-inch guide wire through a 6F percutaneous coronary angioplasty guiding catheter. A 9-mm long, oversized over-the-wire balloon (1.5–2.5 mm) was introduced and inflated and the distal vessel bed was contrasted. After verification of the correct balloon position and inflation, 1–2 ml of the echo contrast agent (Levovist, concentration 350 mg/ml, Schering or Sonovue, Bracco) were injected through the balloon catheter lumen under continuous TTE imaging. Once dye reflux into the left anterior descending (LAD) coronary artery was excluded and if probatory vessel closure by the inflated balloon had resulted in significant LVOT gradient reduction, multiple 0.5-ml alcohol injections were performed. Each injection was performed slowly, over a period of 30 seconds. Special care was taken to avoid leakage of alcohol into the LAD and its major branches. The balloon remained inflated for 10 minutes after the alcohol administration to enhance tissue contact and to exclude alcohol reflux into the LAD. Finally, all the haemodynamic measurements (see below) were repeated. The pacemaker lead was left in situ for at least 48 hours and the patient had a telemetric recording during the whole hospitalisation period.

Haemodynamics and LV function

Left ventricular (LV) function before, during and after the PTSMA procedure was assessed by online LV pressure-volume signals obtained by a 7F combined pressure-conductance catheter (CD Leycom, Zoetermeer, The Netherlands) introduced retrogradely into the LV and placed along the LV long axis. The catheter was connected to a Cardiac Function Lab (CFL-512, CD Leycom) for display and acquisition of pressure-volume loops. The conductance catheter was calibrated by matching the baseline conductance-derived volume signals with end-diastolic and end-systolic volumes obtained by echocardiography before the procedure. Data analysis was performed offline by custom-made software. Haemodynamics and LV function were quantified by cardiac output and stroke volume, end-diastolic and end-systolic volume, LV ejection fraction, end-systolic and end-diastolic pressure, maximal and minimal rate of LV pressure change (dP/dt_{MAX}, $-dP/dt_{MIN}$). The time constant of relaxation (tau) was determined using phase-plot analysis. Stroke work was calculated as the area of the pressure-volume loop. The end-systolic pressure-volume relation (ESPVR) was estimated using a single-beat method adopted from Takeuchi *et al*[16] as illustrated in figure 1. The ESPVR was characterised by its slope E_{ES} (end-systolic elastance) and its position as defined by the volume intercept at 150 mm Hg (ESV_{150}, see fig 1). The end-diastolic stiffness constant K_{ED} was determined by fitting an exponential curve, $P = A.\exp(K_{ED}.V)$, to the diastolic trajectory of the pressure-volume loop, and we also determined end-diastolic stiffness, E_{ED}, as the linear slope of the diastolic trajectory ($P = B + E_{ED}.V$).

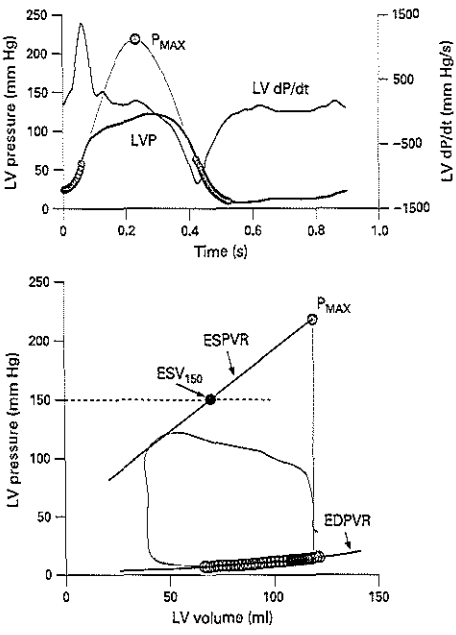


Figure 1 Single-beat estimation of the end-systolic pressure-volume relation (ESPVR) and end-diastolic pressure-volume relation (EDPVR). dP/dt_{MAX}, maximal rate of LV pressure increase; ESV, end-systolic volume; LV, left ventricular; P_{MAX}, isovolumic peak pressure.

Statistical analysis

Continuous variables are shown as mean (SD) and were compared using Student t tests. Categorical variables are presented as counts and percentage and compared with the Fisher's exact test. Differences were considered significant if the p value was <0.05. All statistical tests were two tailed. Statistical analyses were performed by SPSS (version 12.0.1).

RESULTS

Baseline patient characteristics

Baseline clinical and haemodynamic characteristics are presented in tables 1 and 2. Mean age at the time of the procedure was 62 (13) years. Angina occurred in six patients (35%), syncope in three (18%) and dyspnoea was present in eight (47%). All patients were symptomatic despite optimal medical treatment with β-blockers (53%), calcium channel antagonists (59%) and diuretics (35%): eight patients (47%) were in NYHA class III and nine (53%) were in NYHA class II. In this series, no patients were in NYHA class IV. The mean gradient at rest was

Table 1 Baseline patient (n = 17) characteristics

Age, years (mean (SD))	62 (13)
Male	11 (64%)
Female	6 (36%)
Symptoms	
Angina	6 (35%)
Syncope	3 (18%)
Dyspnoea	8 (47%)
Medications	
β-blockers	9 (53%)
Calcium channel antagonists	10 (59%)
Diuretics	6 (35%)
NYHA functional class	
II	9 (53%)
III	8 (47%)
IV	0 (0%)

Original article

Table 2 Baseline (Pre) and post-procedural (Post) haemodynamic measurements (n = 17)

	Pre	Post	p Value
Gradient (mm Hg)	79 (38)	14 (16)	<0.001
Post-extrasystolic gradient (mm Hg)	130 (50)	34 (33)	<0.001
HR (beats/min)	69 (12)	67 (11)	0.326
SV (ml)	86 (28)	81 (38)	0.794
CO (l/min)	6 (2.3)	5.3 (2.5	0.409
SW (l.mm Hg)	10.7 (3.7)	9.2 (4.4)	0.135
ESV (ml)	33 (14)	44 (19)	0.004
EDV (ml)	110 (30)	119 (36)	0.073
EF (%)	78 (9)	67 (13)	<0.001
ESP (mm Hg)	166 (27)	129 (26)	<0.001
EDP (mm Hg)	25 (6)	21 (7)	0.049
LVP_{PEAK} (mm Hg)	187 (32)	147 (24)	<0.001
LVP_{MIN} (mm Hg)	8.1 (3.3)	7.2 (3.7)	0.322
dP/dt_{MAX} (mm Hg/s)	1549 (289)	1438 (244)	0.069
$-dP/dt_{MIN}$ (mm Hg/s)	1611 (248)	1310 (333)	0.001
Tau (ms)	111 (61)	67 (15)	0.011
P_{MAX} (mm Hg)	268 (40)	230 (36)	0.011
E_{ES} (mm Hg/ml)	1.93 (1.16)	1.38 (0.62)	0.041
ESV_{150} (ml)	36 (15)	58 (22)	<0.001
E_{ED} (mm Hg/ml)	0.32 (0.24)	0.19 (0.09)	0.014
K_{ED} (1/ml)	0.025 (0.021)	0.021 (0.019)	0.275

CO, cardiac output; dP/dt_{MAX}, maximal rate of LV pressure increase; $-dP/dt_{MIN}$, maximal rate of LV pressure decline; E_{ED}, diastolic stiffness; E_{ES}, end-systolic elastance (slope of ESPVR); EDP, end-diastolic pressure; EDV, end-diastolic volume; EF, ejection fraction; ESP, end-systolic pressure; ESV, end-systolic volume; ESV_{150}, intercept of ESPVR; HR, heart rate; K_{ED}, diastolic stiffness constant; LVP_{MIN}, minimal LV pressure; LVP_{PEAK}, peak left ventricular (LV) systolic pressure; P_{MAX}, isovolumic peak pressure; SV, stroke volume; SW, stroke work; tau, relaxation time constant.

79 (38) mm Hg, the mean post-extrasystolic gradient was 130 (50) mm Hg and the mean septal thickness was 21.7 (0.5) mm.

Procedural results

An average of 2.0 (0.5) ml of ethanol was injected per patient. In all patients except two, only one septal branch was treated. In eight patients the first septal branch was treated, in six patients the second, in one the third. In two patients both the first and the second septal branches were treated because of incomplete gradient relief after the treatment of the first one. No death or sustained ventricular arrhythmias occurred. Eight patients developed right bundle branch block, which was persistent in four. No patient required permanent pacemaker implantation after the procedure. Acute haemodynamic findings are summarised in figure 2 and table 2. The mean rest and post-extrasystolic gradient were both significantly decreased after the procedure (79 (38) to 14 (16) mm Hg and 130 (50) to 34 (33) mm Hg, respectively, both with p value <0.001). The CO, HR, SV and SW were unchanged. The ESV increased from 33 (14) to 44 (19) ml (p = 0.004); the EDV tended to increase from 110 (30) to 119 (36) ml (p = 0.07) and the ejection fraction significantly decreased from 78% (9%) to 67% (13%) (p<0.001). Both ESP and EDP significantly decreased from 166 (27) to 129 (26) mm Hg (p<0.001) and from 25 (6) to 21 (7) mm Hg, respectively. LVP_{PEAK} decreased from 187 (32) to 147 (24) (p<0.001). LV dP/dt_{MAX} tended to decrease from 1549 (289) to 1438 (244) mm Hg/s (p = 0.069) and $-dP/dt_{MIN}$ significantly decreased from 1611 (248) to 1310 (333) mmHg/s (p = 0.001). Both tau and E_{ED} were reduced from 111 (61) to 67 (15) ms (p = 0.011) and from 0.32 (0.24) to 0.19 (0.09) mm Hg/ml (p = 0.014), respectively. The ESPVR showed a decreased slope (E_{ES} from 1.93 (1.16) to 1.38 (0.62) mm Hg/ml, p = 0.041) and a shift to the right (ESV_{150} from 36 (15) to 58 (22) ml, p<0.001). Figure 3 shows a typical example of pressure-volume loops before and after PTSMA.

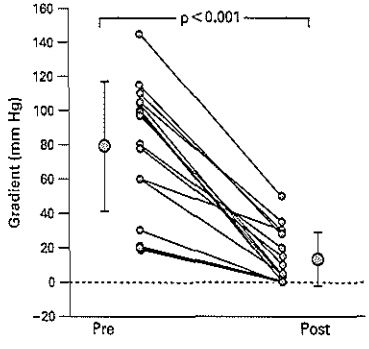


Figure 2 Acute effect of percutaneous transluminal septal myocardial ablation: left ventricular (LV) outflow tract gradient before (Pre) and after (Post) procedure.

DISCUSSION

HOCM was first described in the late 1950s.[15 16] A morphological difference is made between subaortic obstruction and the more rare mid-ventricular obstruction. Symptoms and disease manifestations in patients with HOCM include dyspnoea, angina, palpitations, syncope, heart failure and sudden cardiac death. Obstruction of LVOT, diastolic dysfunction, cardiac ischaemia and rhythm disturbances are the main problems and underlying mechanisms in patients with HOCM.[1 10] Symptomatic patients not only have impaired quality of life but also seem to have an adverse prognosis; the occurrence of atrial fibrillation, ventricular tachycardia[17] and myocardial ischaemia[18] are all prognostically unfavourable factors.

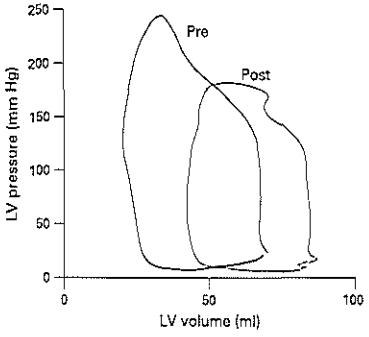


Figure 3 Typical example of pressure-volume loops before (Pre) and after (Post) percutaneous transluminal septal myocardial ablation. LV, left ventricular.

Symptomatic HOCM patients are usually treated first with negatively inotropic substances, especially β-blockers, calcium antagonists like verapamil, or disopyramide.[19] These drugs may favourably modify LV diastolic function through their anti-ischaemic actions although the effect on symptoms and LVOT obstruction is often limited and present only in a select group of patients. Moreover, verapamil may prolong tau and increase filling pressures in some patients. A recent study indicated that disopyramide combined with β-blockers may provide amelioration of symptoms without proarrhythmic effects.[19] Atrioventricular sequential pacing has been applied[20] and was reported to reduce the outflow tract gradient up to 30%, to limit cavity obliteration and reduce systolic pressures probably by inducing dyssynchronous apical contraction,[21] which was leading to a decrease in symptoms in patients without affecting septal thickness.[22] Surgical myectomy has been the therapeutic option of choice for decades since the late 1950s,[4 20] and patients tend to have improved markers of diastolic LV function and a favourable prognosis. Recently, PTSMA has been shown to be an attractive alternative to surgical myectomy. The induction of a limited "therapeutic" infarction as a result of ethanol injection[24] within the hypertrophied septal myocardium leads to localised thinning and regional contractile dysfunction, which expands the left ventricular outflow tract, eliminates or reduces the mitral valve SAM and thus reduces LVOT gradient and the resulting symptoms.[25-28]

Previous echocardiographic and magnetic resonance imaging studies have shown that LVOT gradient reduction is associated with a decreased afterload and an increased cardiac output,[29-31] resulting in a higher diastolic pressure in the aorta along with a lower diastolic pressure in the LV. These changes enhance coronary flow and myocardial perfusion by increasing coronary filling pressure, leading to reduced subendocardial ischaemia and improved LV relaxation.[32 33] Moreover, the gradual regression of hypertrophy and the changes in LV geometry may explain the further long-term improvement in diastolic function.[32-34] Most of these changes are assumed to achieve their maximum effect generally weeks or months after the procedure, but what happens immediately after the procedure is still poorly understood. In the present study we used invasive conductance catheter-derived pressure-volume loops to assess the acute effects of PTSMA on general haemodynamics, and systolic and diastolic LV function. This methodology has been validated extensively[35] and has the unique advantage of providing continuous, online haemodynamics and relatively load-independent indexes of systolic and diastolic LV function.

The results indicate that, despite the acute gradient reduction, general haemodynamics reflected by CO and SW were not greatly affected. However, systolic function was acutely reduced: this was evidenced by a reduced ejection fraction resulting from increased EDV with maintained SV. Consistently, dP/dt_{MAX} decreased, although this effect just failed to reach statistical significance ($p = 0.069$). Since these traditional indexes may be affected by the greatly altered loading conditions we also assessed systolic LV function by the ESPVR, a relatively load-independent relation: the significant reduction in slope and the rightward shift of the ESPVR both clearly indicated a reduction in intrinsic systolic function.

Conversely, diastolic LV function showed an acute improvement: EDP decreased significantly despite the increase in EDV, and tau also improved significantly. In line with these finding, the EDPVR showed a decreased slope indicating improved diastolic compliance. The improved diastolic function and increased EDV (Frank-Starling effect) presumably compensated for the systolic loss and resulted in maintained stroke volume. The reduced systolic function most likely reflects the iatrogenic loss of functional cardiac muscle induced by the alcohol injection. The amount of the loss is related both to the site and the size of the infarct area, which in turn depends on the quantity of ethanol delivered and on the number of septal branches treated. In our series all patients, except two, had a single septal branch treated and the infarct area was similar in all patients (22.4 (6.9) mm^2, evaluated by echocardiography). The acute improvement in diastolic function is in line with previously reported long-term effects. However, whereas long-term improvements may be mainly due to regression of myocardial hypertrophy, the current findings suggest an improvement in intrinsic myocardial function: we speculate that relief of subendocardial ischaemia may partly explain this acute effect. In addition, relaxation is known to be affected by systolic load via changes in intracellular calcium transients.[36] Potentially, acute systolic load reduction may also have improved relaxation via this pathway. Interestingly, $-dP/dt_{MIN}$ was reduced, suggesting a worsening of the isovolumic relaxation. This, however, can be explained because $-dP/dt_{MIN}$ reflects the very early part of diastole, this "active" relaxation phase is largely dependent on systolic properties that, in this acute setting, are iatrogenically depressed.[37 38]

Limitations

Ideally, ESPVR and EDPVR are derived from multiple beats at altered loading conditions. In most pressure-volume loop studies a gradual reduction in preload is induced by balloon occlusion of the inferior vena cava. In the present study group we were hesitant to apply this intervention because these patients with diastolic dysfunction and near cavity obliteration at end-systole have very little reserve capacity and preload reduction was anticipated to result in large pressure drops and unstable haemodynamics. Therefore we applied single-beat methodologies to derive ESPVR and EDPVR. These approaches were previously used and generally found to be reasonable estimates of multi-beat pressure-volume relations.[34 39 40]

In conclusion, our mechanistic findings describe the complex haemodynamic effects acutely induced by PTSMA and help to explain how treatment may result in immediate symptom relief well before remodelling of the LV cavity takes place. PTSMA acutely reduced systolic function but promptly improved diastolic function with maintained general haemodynamics.

Original article

Most previous studies indicated that 3–6 months after the procedure, both systolic and diastolic performance indexes are improved; this difference is probably the result of the influence the tissue loss has on the systolic function in the acute phase while the compensatory and remodelling processes have not yet started. More generally, the present data could be relevant for operative risk assessment, post-procedural patient management and future optimisation of the procedure in high-risk heart failure patients. Our findings suggest that PTSMA can be safely applied in patients with severe heart failure symptoms.

Competing interests: None.

REFERENCES

1. **Maron BJ,** Hypertrophic cardiomyopathy: a systematic review. *JAMA* 2002;**287**:1308–20.
2. **Maron MS,** Olivotto I, Betocchi S, *et al.* Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 2003;**348**:295–303.
3. **Autore C,** Bernabo P, Barilla CS, *et al.* The prognostic importance of left ventricular outflow obstruction in hypertrophic cardiomyopathy varies in relation to the severity of symptoms. *J Am Coll Cardiol* 2005;**45**:1076–80.
4. **Deb SJ,** Schaff HV, Dearani JA, *et al.* Septal myectomy results in regression of left ventricular hypertrophy in patients with hypertrophic obstructive cardiomyopathy. *Ann Thorac Surg* 2004;**78**:2118–22.
5. **Van der Lee C,** ten Cate FJ, *et al.* Percutaneous versus surgical treatment for patients with hypertrophic obstructive cardiomyopathy and enlarged anterior mitral valve leaflets. *Circulation* 2005;**112**:482–8.
6. **Seggewiss H,** Gleichmann U, Faber L, *et al.* Percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: acute results and 3-month follow-up in 25 patients. *J Am Coll Cardiol* 1998;**31**:252–8.
7. **Faber L,** Meissner A, Ziemssen P, *et al.* Percutaneous transluminal septal myocardial ablation for hypertrophic obstructive cardiomyopathy: long term follow up of the first series of 25 patients. *Heart* 2000;**83**:326–31.
8. **Abbas AE,** Brewington SD, Dixon SR, *et al.* Alcohol septal ablation for hypertrophic obstructive cardiomyopathy. *J Interv Cardiol* 2005;**18**:155–62.
9. **Zeng Z,** Wang F, Dou X, *et al.* Comparison of percutaneous transluminal septal myocardial ablation versus septal myectomy for the treatment of patients with hypertrophic obstructive cardiomyopathy—a meta analysis. *Int J Cardiol* 2006;**112**:80–4.
10. **Knight CJ,** Alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Heart* 2006;**92**:1339–44.
11. **Flores-Ramirez R,** Lakkis NM, Middleton KJ, *et al.* Echocardiographic insights into the mechanisms of relief of left ventricular outflow tract obstruction after nonsurgical septal reduction therapy in patients with hypertrophic obstructive cardiomyopathy. *J Am Coll Cardiol* 2001;**37**:208–14.
12. **Oomman A,** Ramachandran P, Subramanyan K, *et al.* Percutaneous transluminal septal myocardial ablation in drug-resistant hypertrophic obstructive cardiomyopathy: 18-month follow-up results. *J Invasive Cardiol* 2001;**13**:526–30.
13. **Faber L,** Welge D, Fassbender D, *et al.* One-year follow-up of percutaneous septal ablation for symptomatic hypertrophic obstructive cardiomyopathy in 312 patients: predictors of hemodynamic and clinical response. *Clin Res Cardiol* 2007;**96**:964–73.
14. **Takeuchi M,** Igarashi Y, Tomimoto S, *et al.* Single-beat estimation of the slope of the end-systolic pressure-volume relation in the human left ventricle. *Circulation* 1991;**83**:202–12.
15. **Morrow AG,** Brockenbrough EC. Surgical treatment of idiopathic hypertrophic subaortic stenosis: technique and hemodynamic results of subaortic ventriculotomy. *Ann Surg* 1961;**154**:181.
16. **Teare RD.** Asymmetrical hypertrophy of the heart in young adults. *Br Heart J* 1958;**20**:1–8.
17. **Spirito P,** Rapezzi C, Autore C, *et al.* Prognosis of asymptomatic patients with hypertrophic cardiomyopathy and nonsustained ventricular tachycardia. *Circulation* 1994;**90**:2743–7.
18. **Chang AC,** McAreavey D, Fananapazir L. Identification of patients with hypertrophic cardiomyopathy at high risk for sudden death. *Curr Opin Cardiol* 1995;**10**:9–15.
19. **Sherrid MV,** Barac I, McKenna WJ, *et al.* Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005;**45**:1251–8.
20. **Meisel E,** Rouwolf T, Burghardt M, *et al.* Pacemaker therapy of hypertrophic obstructive cardiomyopathy. Pacing in Cardiomyopathy Study Group. *Herz* 2000;**25**:481–6.
21. **Pak PH,** Maughan WL, Baughman KL, *et al.* Mechanism of acute mechanical benefit from VDD pacing in hypertrophied heart: similarity of responses in hypertrophic cardiomyopathy and hypertensive heart disease. *Circulation* 1998;**98**:242–8.
22. **Mehri M,** Ichiki T, Kuga T, *et al.* Evidence for anti-ischemic effect of dual-chamber pacing in patients with the obstructive form of hypertrophic cardiomyopathy. *Jpn Heart J* 2003;**44**:587–92.
23. **Ralph-Edwards A,** Woo A, McCrindle BW, *et al.* Hypertrophic obstructive cardiomyopathy: comparison of outcomes after myectomy or alcohol ablation adjusted by propensity score. *J Thorac Cardiovasc Surg* 2005;**129**:351–8.
24. **Boggish AL,** Smith RN, Palacios I, *et al.* Pathological effects of alcohol septal ablation for hypertrophic obstructive cardiomyopathy. *Heart* 2006;**92**:1773–8.
25. **Yeorger DM,** Picard MH, Palacios IF, *et al.* Time course of pressure gradient response after first alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Am J Cardiol* 2006;**97**:1511–4.
26. **Song JM,** Fukuda S, Lever HM, *et al.* Asymmetry of systolic anterior motion of the mitral valve in patients with hypertrophic obstructive cardiomyopathy: a real-time three-dimensional echocardiographic study. *J Am Soc Echocardiogr* 2006;**19**:1129–35.
27. **Jassal DS,** Neilan TG, Fifer MA, *et al.* Sustained improvement in left ventricular diastolic function after alcohol septal ablation for hypertrophic obstructive cardiomyopathy. *Eur Heart J* 2006;**27**:1805–10.
28. **Airoldi F,** Di Mario C, Catanoso A, *et al.* Progressive decrease of outflow gradient and septum thickness after percutaneous alcoholization of the interventricular septum in hypertrophic obstructive cardiomyopathy. *Ital Heart J* 2000;**1**:200–6.
29. **De Gregorio C,** Recupero A, Grimaldi P, *et al.* Can transthoracic live 3-dimensional echocardiography improve the recognition of midventricular obliteration in hypertrophic obstructive cardiomyopathy? *J Am Soc Echocardiogr* 2006;**19**:1190 e1–4.
30. **Sitges M,** Qin JX, Lever HM, *et al.* Evaluation of left ventricular outflow tract area after septal reduction in obstructive hypertrophic cardiomyopathy: a real-time 3-dimensional echocardiographic study. *Am Heart J* 2005;**150**:852–8.
31. **Amano Y,** Takayama M, Amano M, *et al.* MRI of cardiac morphology and function after percutaneous transluminal septal myocardial ablation for hypertrophic obstructive cardiomyopathy. *Am J Roentgenol* 2004;**182**:523–7.
32. **Sitges M,** Shiota T, Lever HM, *et al.* Comparison of left ventricular diastolic function in obstructive hypertrophic cardiomyopathy in patients undergoing percutaneous septal alcohol ablation versus surgical myotomy/myectomy. *Am J Cardiol* 2003;**91**:817–21.
33. **Veselka J,** Honek T. Early remodelling of left ventricle and improvement of myocardial performance in patients after percutaneous transluminal septal myocardial ablation for hypertrophic obstructive cardiomyopathy. *Int J Cardiol* 2003;**88**:27–32.
34. **Yacoub MH.** Surgical versus alcohol septal ablation for hypertrophic obstructive cardiomyopathy: the pendulum swings. *Circulation* 2005;**112**:450–2.
35. **Burkhoff D,** Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. *Am J Physiol Heart Circ Physiol* 2005;**289**:H501–12.
36. **Gillebert TC,** Leite-Moreira AF, De Hert SG. Load dependent diastolic dysfunction in heart failure. *Heart Fail Rev* 2000;**5**:345–55.
37. **Brutsaert DL,** Diastolic heart function and dysfunction. *Rev Port Cardiol* 1999;**18**(Suppl 5):V11–5.
38. **Brutsaert DL,** Sys SU. Relaxation and diastole of the heart. *Physiol Rev* 1989;**69**:1228–315.
39. **Brimioulle S,** Wauthy P, Ewalenko P, *et al.* Single-beat estimation of right ventricular end-systolic pressure-volume relationship. *Am J Physiol Heart Circ Physiol* 2003;**284**:H1625–30.
40. **Klotz S,** Hay I, Dickstein ML, *et al.* Single-beat estimation of end-diastolic pressure-volume relationship: a novel method with potential for noninvasive application. *Am J Physiol Heart Circ Physiol* 2006;**291**:H403–12.

CHAPTER 18

EFFECTS OF PERCUTANEOUS TRANSLUMINAL SEPTAL MYOCARDIAL ABLATION FOR OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY ON SYSTOLIC AND DIASTOLIC LEFT VENTRICULAR FUNCTION ASSESSED BY PRESSURE-VOLUME LOOPS

Effects of Percutaneous Transluminal Septal Myocardial Ablation for Obstructive Hypertrophic Cardiomyopathy on Systolic and Diastolic Left Ventricular Function Assessed by Pressure–Volume Loops

Emanuele Meliga, MD[a,c], Paul Steendijk, PhD[b], Marco Valgimigli, MD, PhD[a], Folkert J. Ten Cate, MD, PhD[a], and Patrick W. Serruys, MD, PhD[a,*]

The aim of the present study was to determine the long-term effects of percutaneous transluminal septal myocardial ablation (PTSMA) on systolic and diastolic left ventricular (LV) functions in patients with obstructive hypertrophic cardiomyopathy (HC). Ten consecutive patients with symptomatic HC despite optimal medical treatment were referred for PTSMA at our center. LV systolic and diastolic functions were assessed by online LV pressure–volume loops obtained by conductance catheter at baseline and at 6 months after the procedure. At follow-up, the mean gradients at rest and after extrasystole were significantly decreased compared with baseline (88 ± 29 to 21 ± 11 mm Hg and 130 ± 50 to 35 ± 22 mm Hg, respectively, $p < 0.01$ for the 2 comparisons). End-systolic and end-diastolic pressures significantly decreased ($p < 0.01$), whereas end-systolic and end-diastolic LV volumes significantly increased ($p < 0.01$ for the 2 comparisons). Cardiac output and stroke volume were unchanged, as were ejection fraction ($p = 0.25$) and maximum dP/dt ($p = 0.13$). The slope of the end-systolic pressure–volume relation was not decreased, indicating a preserved contractility. The relaxation constant time, end-diastolic stiffness, projected volume of the end-diastolic pressure–volume relation at 30 mm Hg, and diastolic stiffness constant showed a significant improvement of active and passive myocardial diastolic properties. In conclusion, PTSMA is an effective method in the treatment of symptomatic patients with HC. At 6-month follow-up, the LV–aortic gradient was decreased and active and passive LV diastolic properties were increased. Myocardial contractility was not decreased and general hemodynamics was maintained. (Am J Cardiol 2008;101:1179–1184)

Long-term clinical observations of patients treated with percutaneous transluminal septal myocardial ablation (PTSMA) have shown significant and sustained decreases in left ventricular (LV) outflow tract pressure gradients and improvement of symptoms,[1,2] but thus far, complete information about the long-term changes in systolic and diastolic LV functions after PTSMA are lacking. The aim of this study was to assess the long-term hemodynamic effects of PTSMA in a single center's population with obstructive hypertrophic cardiomyopathy (HC) by LV pressure–volume conductance catheter (pressure–volume loops).

Methods

The study population consisted of 10 consecutive patients with symptomatic obstructive HC despite optimal medical treatment who were referred for PTSMA at our center. The HC diagnosis was based on typical clinical, echocardiographic, and angiocardiographic findings. Inclusion criteria were New York Heart Association functional classes II to IV, LV outflow tract gradient >50 mm Hg at rest or >100 mm Hg at provocation (after extrasystole, isoproterenol, or Valsalva maneuver), septal thickness >15 mm, LV outflow tract diameter <7 mm, and systolic anterior motion of the anterior mitral leaflet. Patients with concomitant cardiac abnormalities suitable for surgery were excluded. The institutional review committee of the Erasmus Medical Centre approved the study protocol and all patients provided informed consent before participation.

Briefly, 2 catheters were placed in the left ventricle and the ascending aorta to record baseline hemodynamic data (see below), including LV outflow tract gradient at rest and at provocation with the Valsalva maneuver. Intraprocedural myocardial contrast transthoracic echocardiography was performed to determine the target vessel. A 9-mm–long, oversized, over-the-wire balloon (1.5 to 2.5 mm) was introduced and inflated in the target vessel and 1 to 2 ml of echocardiographic contrast agent (Levovist, concentration 350 mg/ml, Shering or Sonovue, Bracco, Italy) was injected through the balloon catheter lumen under continuous echocardiographic imaging. Once dye reflux into the left anterior

[a]Department of Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, and [b]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; and [c]Department of Interventional Cardiology, S. Giovanni Battista Hospital, University of Turin, Turin, Italy. Manuscript received October 12, 2007; revised manuscript received and accepted December 9, 2007.

*Corresponding author: Tel: 31-10-463-5260; fax: 31-10-436-9154.
E-mail address: p.w.j.c.serruys@erasmusmc.nl (P.W. Serruys).

descendant artery was excluded and probatory vessel closure by the inflated balloon resulted in significant LV outflow tract gradient decrease, multiple 0.5-ml alcohol injections were performed (ethanol 1.97 ± 0.51 ml per patient on average). Each injection was performed over a period of 30 seconds. In all except 2 patients, only 1 septal branch was treated (first septal branch, 6 patients; second septal branch, 2 patients; first and second septal branches, 2 patients). The balloon remained inflated for 10 minutes after alcohol administration to exclude alcohol reflux into the left anterior descendant artery. All hemodynamic measurements were repeated. A 6F transfemoral temporary pacemaker was positioned in the right ventricle and left in situ for ≥48 hours. Procedures were considered successful when postprocedural pressure gradient at rest was <16 mm Hg or when the percent pressure gradient decrease after the procedure was >50%.[3,4]

LV dynamic data were recorded before, during, and after the PTSMA procedure by online LV pressure–volume signals obtained by a 7F combined pressure-conductance catheter (CD Leycom, Zoetermeer, The Netherlands) introduced into the left ventricle through the femoral artery. The catheter was connected to a Cardiac Function Lab (CFL-512, CD Leycom) for display and acquisition of pressure–volume loops. A Swan-Ganz catheter was placed in the pulmonary artery through the femoral vein. Parallel conductance and cardiac output were determined by multiple injections of hypersaline solution and thermodilution to calibrate the volume signals of the conductance catheter.[5,6] Postextrasystolic gradient was determined by induction of extrasystoles from a pacemaker wire. Data analysis was performed offline by custom-made software.

Hemodynamics and LV function were quantified by cardiac output and stroke volume, end-diastolic and end-systolic volumes, LV ejection fraction, end-systolic and end-diastolic pressures, and maximal and minimal rates of LV pressure change (dP/dt). The isovolumic relaxation period (defined as the period between the time point of minimal dP/dt and the time point where dP/dt reached 10% of minimal dP/dt) was analyzed using phase-plot analysis and the time constant of relaxation was then determined. The end-systolic pressure–volume relation (ESPVR) was estimated using the method adopted by Takeuchi et al[7] and the change in contractility was determined by the change of the slope of the ESPVR line and its position, as defined by the projected volume value of the relation at 200 mm Hg (Figure 1). The end-diastolic pressure–volume relation (EDPVR) was estimated using the method adopted by Klotz et al.[8] The change in diastolic distensibility was calculated by the left to rightward shift of the EDPVR at the fixed pressure level of 30 mm Hg. The end-diastolic stiffness constant was determined by fitting a exponential curve, P (pressure) = A (paramete value) × exp(end-diastolic stiffness constant × volume), to the diastolic trajectory of the pressure–volume loop (Figure 2), and we determined end-diastolic stiffness as the end-diastolic pressure/end-diastolic volume ratio.[9]

All patients were monitored in the coronary care unit for ≥48 hours. After discharge, patients were suggested to continue medical treatment with a cardioselective β blocker or with a low dose of verapamil. After 6 months, all patients underwent invasive follow-up by LV pressure–volume conductance catheter.

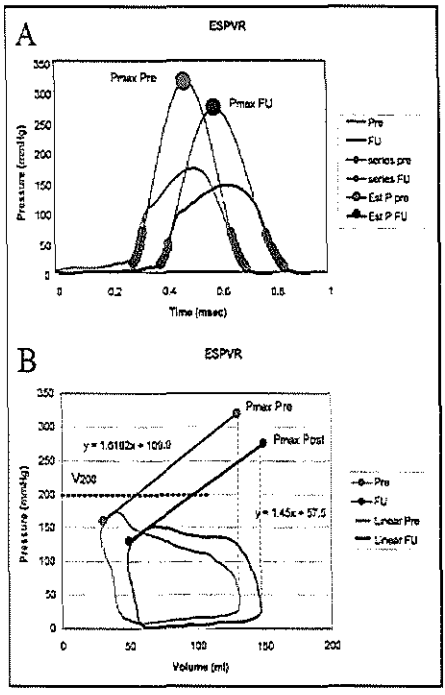


Figure 1. Single-beat estimation of ESPVR using the method adopted by Takeuchi et al.[7] *(A)* Point series representing isovolumic contraction and relaxation phases are selected and plotted on the pressure curve. Estimated theoretical maximal pressure reached in the left ventricle during an isovolumic beat (Pmax) is estimated by fitting a fifth-order curve to the point series. *(B)* ESPVR slope is represented by the equation of the line drawn from Pmax to the left upper corner of the pressure–volume loop of a real ejecting beat. FU = 6-month follow-up; LVP = LV pressure; Pre = baseline; V_{200} = volume intercept at 200 mm Hg.

Continuous variables are presented as mean ± SD and were compared using Student's unpaired and paired *t* tests, when appropriate. Categorical variables are presented as counts and percentages and were compared with Fisher's exact test. Correlations between variables were tested by Pearson analysis. Differences were considered significant if the p value was <0.05. All statistical tests were 2-tailed. Data processing and statistical analyses were performed with SPSS 12.0.1 (SPSS, Inc., Chicago, Illinois).

Results

Baseline and 6-month follow-up clinical characteristics and hemodynamic measurements are presented in Table 1. Mean age at the time of the procedure was 61 ± 11 years. Angina was the principal manifestation in 3 patients (30%), syncope in 2 (20%), and dyspnea in 5 (50%). Despite optimal medical treatment, 4 patients (40%) were in New York Heart Association class III and 6 (60%) were in New York Heart Association class II. Mean gradient at rest was

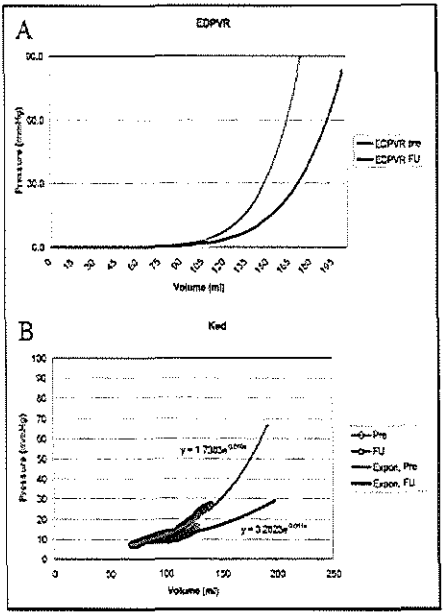


Figure 2. Single-beat estimation of EDPVR and end-diastolic constant (K_{ED}). *(A)* EDPVR is estimated using the method adopted by Klotz et al.[8] EDP = α*EDV^β represents the equation of the estimated exponential curve. Alpha (α) and beta (β), obtained by a sequence of calculations from a single set of pressure and volume values, represent coefficients of the estimated curve. *(B)* K_{ED} determination by exponential fitting. For more details, see Methods. V_{30} = volume intercept at 30 mm Hg. Other abbreviations as in Figure 1.

88 ± 29 mm Hg and mean postextrasystolic gradient was 130 ± 50 mm Hg.

Heart rate at time of data acquisition was similar in at baseline and at 6-month follow-up. Mean gradients at rest and after extrasystole were significantly decreased at follow-up. Stroke volume, cardiac output, and ejection fraction did not differ significantly. End-systolic and end-diastolic volumes increased and end-systolic, end-diastolic, and LV peak pressures significantly decreased after the procedure. LV maximal and minimal dP/dt values were not significantly changed. Slope of the ESPVR line remained approximately constant and relaxation time constant and end-diastolic and end-diastolic stiffness constants were decreased. Projected volumes of ESPVR at 200 mm Hg and EDPVR at 30 mm Hg were significantly increased. Figure 3 shows a typical example of pressure–volume loops before the procedure and at 6-month follow-up.

Discussion

Results of the present study indicated that, at 6-month follow-up, (1) LV outflow tract gradient remained low at rest and at provocation, (2) general hemodynamics and intrinsic myocardial systolic properties were not affected, and (3) diastolic function was significantly improved.

Short- and mid-term results of PTSMA are excellent for the decrease of LV outflow tract gradient obstruction. Previous studies have reported that, at 3 months, mean pressure gradients at rest and at provocation (postextrasystolic gradient) were significantly decreased,[10] showing a persistent 75% to 80% decrease of LV outflow tract gradient compared with baseline. Consistent with these data, in our study at 6 months, mean LV outflow tract gradient was 21 ± 11 mm Hg, which is an 86% decrease compared with baseline, whereas postextrasystolic gradient was persistently decreased by 73% (from 130 ± 50 to 35 ± 22 mm Hg), suggesting the efficacy of this nonsurgical approach over time. Moreover, LV outflow tract gradient measured by echocardiography and simultaneous ventricular/aortic pressure sampling showed a stable improvement and a limited recurrence of LV outflow tract obstruction in studies with even longer follow-up.[11]

General hemodynamics and systolic function have been reported to deteriorate soon after the procedure, but at mid-term follow-up (3 months), several noninvasive studies have reported ejection fraction and cardiac index not to be significantly decreased.[12,13] The acute changes most likely reflect iatrogenic loss of functional cardiac muscle induced by alcohol injection. The amount of the loss is related to the site and size of the infarct area, which in turn depends on the quantity of alcohol delivered and on the precision of the alcohol delivery in the target region. Use of an echocardiographic contrast–guided approach to identify the target vessel and probe the correct vessel closure before the alcohol injections (see Methods) is of crucial importance to avoid large LV infarctions and subsequent risks of hemodynamic impairment and arrhythmias.

In our series, general hemodynamics represented by cardiac output and stroke volume was not affected at 6-month follow-up. Increase of end-systolic volume was accompanied by a similar increase of end-diastolic volume that, thanks to the Frank-Starling effect, most likely compensated for the systolic loss and resulted in maintained stroke volume. Systolic function, represented by ejection fraction and maximal dP/dt, did not show a significant decrease. Because these systolic indexes are known to be affected by different loading conditions, the intrinsic systolic properties of the left ventricle were also assessed by ESPVR, a relatively load-independent index of contractility.[14] In our series, there was no significant change in ESPVR slope, thus indicating a preserved intrinsic systolic function. The rightward shift of the ESPVR, generally representing a worsening of systolic properties, in these patients had a limited significance because it was partially dependent on the modifications of LV hemodynamics occurring after the procedure (decrease of mitral regurgitation, increase of end-systolic volume, and concomitant increase of end-diastolic volume).

The LV outflow tract gradient decrease is associated with a decreased afterload and an increased cardiac output,[15–17] resulting in a higher diastolic pressure in the aorta, a lower diastolic pressure in the left ventricle, and a higher coronary filling pressure. The increased myocardial perfusion, gradual regression of hypertrophy, and subsequent changes in LV geometry[18,19] are considered the main causes of the long-term improvement of diastolic function.

In our series, LV diastolic function showed significant changes: end-diastolic pressure decreased significantly de-

Table 1
Baseline patient characteristics and hemodynamic measurements at baseline and FU

Patient No.	Age (yrs)/Sex	Symptom	Medications	NYHA Class		Gradient (mm Hg)	PES Gradient (mm Hg)	HR (beats/min)	SV (ml)	CO (L/min)	ESV (ml)
1	48/F	D	C, Di	III	Baseline	103	176	60	99	6	37
					FU	16	21	60	110	6.6	31
2	50/F	D	C	II	Baseline	81	112	49	96	4.7	28
					FU	22	40	60	88	5.3	58
3	52/F	D	B, C	II	Baseline	77	164	76	106	8.1	46
					FU	26	53	82	109	8.9	47
4	53/M	D	B, C	II	Baseline	57	59	60	107	6.4	52
					FU	9	11	65	101	6.6	68
5	54/M	D	B, Di	III	Baseline	145	199	75	130	9.2	30
					FU	41	68	58	128	7.3	43
6	66/M	S	B, C	II	Baseline	89	144	70	102	7.2	24
					FU	31	58	64	98	6.2	45
7	68/M	A	B, C	II	Baseline	59	68	57	113	6.5	32
					FU	10	13	59	81	5.3	50
8	70/M	A	B, Di	III	Baseline	75	117	83	115	9.3	38
					FU	8	11	78	118	9.2	49
9	71/M	A	B, Di	III	Baseline	124	179	67	78	5.2	35
					FU	30	49	74	103	7.7	33
10	77/F	S	B, C	II	Baseline	68	84	85	109	9	31
					FU	19	23	56	97	5.5	59
Mean ± SD	61 ± 11				Baseline	88 ± 29	130 ± 50	68 ± 11	105 ± 14	7.2 ± 1.7	35 ± 8
					FU	21 ± 11	35 ± 22	66 ± 9	103 ± 14	6.9 ± 1.5	45 ± 11
					p value	<0.01	<0.01	0.52	0.79	0.56	<0.01

A = angina; B = β blockers; C = calcium antagonists; CO = cardiac output; D = dyspnea; Di = diuretics; dP/dt_{max} = maximal rate of LV pressure increase; dP/dt_{min} = maximal rate of LV pressure decrease; EDP = end-diastolic pressure; EDV = end-diastolic volume; E_{ED} = diastolic stiffness; E_{ES} = slope of ESPVR; EF = ejection fraction; ESP = end-systolic pressure; ESV = end-systolic volume; FU = 6-month follow-up; HR = heart rate; K_{ED} = diastolic stiffness constant; LVP_{PEAK} = peak LV systolic pressure; NYHA = New York Hear Association; PES = postextrasystolic; SV = stroke volume;

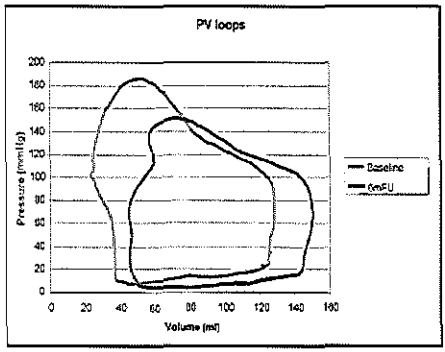


Figure 3. Typical example of pressure–volume (PV) loops before the procedure *(gray line)* and at 6-month follow-up *(black line)*. Abbreviations as in Figure 1.

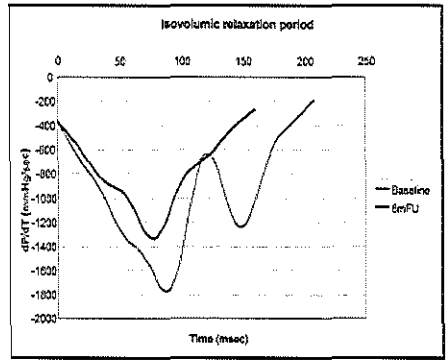


Figure 4. Changes of dP/dt over time during the isovolumic relaxation period before PTSMA *(dashed line)* and at 6-month follow-up *(dotted line)* represent a typical example of dP/dt biphasic pattern.

spite the increase in end-diastolic volume and end-diastolic and end-diastolic stiffness constants decreased significantly. In line with these findings, EDPVR showed a decreased slope and projected volume of EDPVR at 30 mm Hg significantly increased, indicating improved diastolic compliance and distensibility. Previous echocardiographic studies evaluating active myocardial relaxation found that active myocardial relaxation properties were abnormally altered in patients with HC but normalized after PTSMA at 1- and 2-year follow-ups.[20,21] In line with these results, our study showed that active relaxation properties of the myocardium improved after the procedure, as confirmed by the significant decrease of the relaxation time constant. More interestingly, analyzing selectively the isovolumic relaxation phase, we noticed that changes due to the procedure were quantitative (decrease of relaxation time constant and minimal dP/dt) and qualitative. At baseline, the isovolumic relaxation curve showed an interesting biphasic trend, with an early and steep slowdown phase followed by a significant increase in dP/dt and a second slowdown phase. This peculiar trend, markedly evident in 8 of 10 patients, disappeared after the procedure (Figure 4). The mechanisms responsible

Table 1
Continued

EDV (ml)	EF (%)	ESP (mm Hg)	EDP (mm Hg)	LVP_{PEAK} (mm Hg)	dP/dt_{max} (mm Hg/s)	dP/dt_{min} (mm Hg/s)	Tau (ms)	E_{ES} (mm Hg/ml)	V_{200} (ml)	E_{ED} (mm Hg/ml)	V_{30} (ml)	K_{ED} (1/ml)
138	71	186	24	195	1199	1601	92	1.97	51	0.174	140	0.019
140	78	181	19	185	1495	1355	76	1.84	67	0.136	164	0.013
124	77	170	20	190	1150	1320	96	0.82	42	0.160	131	0.019
147	60	115	11	152	1092	1663	60	0.84	90	0.075	170	0.015
150	70	166	18	185	1975	1838	76	1.77	66	0.120	156	0.021
156	80	124	19	149	1576	1710	52	1.45	132	0.122	165	0.020
160	67	123	15	165	1404	1475	104	1.21	71	0.094	164	0.015
169	60	121	11	150	1434	1169	72	1.01	108	0.066	178	0.012
159	79	207	24	212	1704	1630	108	2.25	34	0.152	162	0.014
169	79	113	20	150	1630	1306	56	2.04	115	0.118	171	0.014
125	81	168	17	183	1751	1660	84	2.30	43	0.136	129	0.018
144	68	141	14	166	1516	1490	36	2.14	100	0.097	166	0.012
140	77	142	17	168	1691	1613	80	1.65	60	0.121	145	0.017
141	64	112	12	144	1428	1312	44	1.43	96	0.085	170	0.011
153	75	150	25	179	2199	1696	72	1.53	68	0.161	172	0.016
168	69	139	29	133	2172	1568	40	1.38	98	0.175	171	0.019
112	69	193	34	207	1463	1559	108	0.88	47	0.304	122	0.024
136	76	112	9	130	1393	1352	56	0.92	106	0.070	167	0.021
140	77	142	28	180	1722	1364	96	1.80	65	0.200	144	0.018
157	62	113	15	160	1546	1568	72	1.41	105	0.096	162	0.012
140 ± 16	75 ± 4	164 ± 26	22 ± 6	186 ± 15	1625 ± 328	1575 ± 155	92 ± 13	1.61 ± 0.52	55 ± 12	0.17 ± 0.6	146 ± 16	0.018 ± 0.002
152 ± 13	70 ± 8	127 ± 21	16 ± 6	152 ± 16	1528 ± 270	1449 ± 177	56 ± 13	1.45 ± 0.47	101 ± 16	0.1 ± 0.04	168 ± 4	0.014 ± 0.003
<0.01	0.25	<0.01	<0.01	<0.01	0.13	0.24	<0.01	0.37	<0.01	<0.01	<0.01	<0.01

for these alterations of the active relaxation phase in this setting are not clear. Previous studies have described a similar biphasic curve in patients with aortic stenosis[22] and during the isovolumic contraction phase, attributing the cause of this pattern to the asynchrony of some LV segments during this phase.[23] Other reports have demonstrated that increased coronary vascular resistance,[24] increased wall stress, and myocyte disarray[25] may lead to diastolic LV asynchrony and delayed relaxation. Moreover, it has been reported that, although myocardial systolic torsion is greater in patients affected by HC than without HC, the uncoiling of the myocardium occurred abnormally and was shown to be significantly delayed and depressed.[26–28] We speculate that this biphasic pattern of relaxation may be the expression of the overmentioned anatomic and hemodynamic alterations. The reinstating of normal hemodynamic conditions and gradual regression of LV hypertrophy after PTSMA may therefore explain the drastic "normalization" of the isovolumic relaxation curve pattern.

Ideally, ESPVR and EDPVR are derived from multiple beats at altered loading conditions, usually by balloon occlusion of the inferior vena cava. In the present study group we were hesitant to apply this intervention because patients with HOCM have very little reserve capacity and preload decrease was anticipated to result in large pressure decreases and unstable hemodynamics. Therefore we applied single-beat methods to derive ESPVR and EDPVR.

1. Oomman A, Ramachandran P, Subramanyan K, Kalarickal MS, Osman MN. Percutaneous transluminal septal myocardial ablation in drug-resistant hypertrophic obstructive cardiomyopathy: 18-month follow-up results. *J Invasive Cardiol* 2001;13:526–530.
2. Guo H, Wang J, Chen J, Shan J, Lee JD, Ueda T. Percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: acute results and three-year noninvasive follow-up in 18 patients. *Can J Cardiol* 2004;20:779–782.
3. Lakkis NM, Nagueh SF, Kleiman NS, Killip D, He ZX, Verani MS, Roberts R, Spencer WH. Echocardiography-guided ethanol septal reduction for hypertrophic obstructive cardiomyopathy. *Circulation* 1998;98:1750–1755.
4. Nagueh SF, Lakkis NM, Middleton KJ, Spencer WH III, Zoghbi WA, Quinones MA. Doppler estimation of left ventricular filling pressures in patients with hypertrophic cardiomyopathy. *Circulation* 1999;99:254–261.
5. Baan J, van der Velde ET, de Bruin HG, Smeenk GJ, Koops J, van Dijk AD, Temmerman D, Senden J, Buis B. Continuous measurement of left ventricular volume in animals and humans by conductance catheter. *Circulation* 1984;70:812–823.
6. Steendijk P, Staal E, Jukema JW, Baan J. Hypertonic saline method accurately determines parallel conductance for dual-field conductance catheter. *Am J Physiol Heart Circ Physiol* 2001;281:755–763.
7. Takeuchi M, Igarashi Y, Tomimoto S, Odake M, Hayashi T, Tsukamoto T, Hata K, Takaoka H, Fukuzaki H. Single-beat estimation of the slope of the end-systolic pressure–volume relation in the human left ventricle. *Circulation* 1991;83:202–212.
8. Klotz S, Hay I, Dickstein ML, Yi GH, Wang J, Maurer MS, Kass DA, Burkhoff D. Single-beat estimation of end-diastolic pressure–volume relationship: a novel method with potential for noninvasive application. *Am J Physiol Heart Circ Physiol* 2006;291:403–412.
9. Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure–volume analysis: a guide for clinical, translational, and basic researchers. *Am J Physiol Heart Circ Physiol* 2005;289:501–512.
10. Qin JX, Shiota T, Lever HM, Kapadia SR, Sitges M, Rubin DN, Bauer F, Greenberg NL, Agler DA, Drinko JK, et al. Outcome of patients with hypertrophic obstructive cardiomyopathy after percutaneous

transluminal septal myocardial ablation and septal myectomy surgery. *J Am Coll Cardiol* 2001;38:1994–2000.
11. Lakkis NM, Nagueh SF, Dunn JK, Killip D, Spencer WH. Nonsurgical septal reduction therapy for hypertrophic obstructive cardiomyopathy: one-year follow-up. *J Am Coll Cardiol* 2000;36:852–855.
12. Gietzen FH, Leuner CJ, Raute-Kreinsen U, Dellmann A, Hegselmann J, Strunk-Mueller C, Kuhn HJ. Acute and long-term results after transcoronary ablation of septal hypertrophy (TASH). Catheter interventional treatment for hypertrophic obstructive cardiomyopathy. *Eur Heart J* 1999;20:1342–1354.
13. Veselka J, Honek T. Early remodelling of left ventricle and improvement of myocardial performance in patients after percutaneous transluminal septal myocardial ablation for hypertrophic obstructive cardiomyopathy. *Int J Cardiol* 2003;88:27–32.
14. Grossman W, Braunwald E, Mann T, McLaurin LP, Green LH. Contractile state of the left ventricle in man as evaluated from end-systolic pressure–volume relations. *Circulation* 1977;56:845–852.
15. de Gregorio C, Recupero A, Grimaldi P, Coglitore S. Can transthoracic live 3-dimensional echocardiography improve the recognition of midventricular obliteration in hypertrophic obstructive cardiomyopathy? *J Am Soc Echocardiogr* 2006;19:1190–1194.
16. Veselka J, Prochazkova S, Bolomova-Homolova I, Duchonova R, Tesar D. Effects of alcohol septal ablation for hypertrophic obstructive cardiomyopathy on Doppler Tei index: a midterm follow-up. *Echocardiography* 2005;22:105–109.
17. Mustafa MU, Chen C, Cohen M. Hypertrophic obstructive cardiomyopathy in the era of cardiac MRI. *J Invasive Cardiol* 2004;16:340–345.
18. Sitges M, Shiota T, Lever HM, Qin JX, Bauer F, Drinko JK, Agler DA, Martin MG, Greenberg NL, Smedira NG, et al. Comparison of left ventricular diastolic function in obstructive hypertrophic cardiomyopathy in patients undergoing percutaneous septal alcohol ablation versus surgical myotomy/myectomy. *Am J Cardiol* 2003;91:817–821.
19. Veselka J, Honek T. Early remodelling of left ventricle and improvement of performance in patients after percutaneous transluminal septal myocardial ablation for hypertrophic obstructive cardiomyopathy. *Int J Cardiol* 2003;88:27–32.
20. Jassal DS, Neilan TG, Fifer MA, Palacios IF, Lowry PA, Vlahakes GJ, Picard MH, Yoerger DM. Sustained improvement in left ventricular diastolic function after alcohol septal ablation for hypertrophic obstructive cardiomyopathy. *Eur Heart J* 2006;27:1805–1810.
21. Nishihara K, Mikami T, Takatsuji H, Onozuka H, Saito N, Yamada S, Ursawa K, Kitabatake A. Usefulness of early diastolic flow propagation velocity measured by color M-mode Doppler technique for the assessment of left ventricular diastolic function in patients with hypertrophic cardiomyopathy. *J Am Soc Echocardiogr* 2000;13:801–808.
22. Eichhorn P, Grimm J, Koch R, Hess O, Carroll J, Krayenbuehl HP. Left ventricular relaxation in patients with left ventricular hypertrophy secondary to aortic valve disease. *Circulation* 1982;65:1395–1404.
23. Serruys PW, Wijns W, van den Brand M, Meij S, Slager C, Schuurbiers JC, Hugenholtz PG, Brower RW. Left ventricular performance, regional blood flow, wall motion, and lactate metabolism during transluminal angioplasty. *Circulation* 1984;70:25–36.
24. Cannon RO III, Rosing DR, Maron BJ, Leon MB, Bonow RO, Watson RM, Epstein SE. Myocardial ischemia in patients with hypertrophic cardiomyopathy: contribution of inadequate vasodilator reserve and elevated left ventricular filling pressures. *Circulation* 1985;71:234–243.
25. Piloro JS, Hutchins GM, Moore W, Weisfeldt ML. Myocyte disarray develops in papillary muscles released from normal tension after mitral valve replacement. *Circulation* 1982;66:841–846.
26. Robinson TF, Factor SM, Sonnenblick EH. The heart as a suction pump. *Sci Am* 1986;254:84–91.
27. Ashikaga H, Criscione JC, Omens JH, Covell JW, Ingels NB. Transmural left ventricular mechanics underlying torsional recoil during relaxation. *Am J Physiol Heart Circ Physiol* 2004;286:640–647.
28. Young AA, Kramer CM, Ferrari VA, Axel L, Reichek N. Three-dimensional left ventricular deformation in hypertrophic cardiomyopathy. *Circulation* 1994;90:854–867.

CHAPTER 19

ACUTE HEMODYNAMIC CHANGES IN PERCUTANEOUS TRANSLUMINAL SEPTAL COIL EMBOLIZATION FOR HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

CASE STUDY

www.nature.com/clinicalpractice/cardio

Acute hemodynamic changes in percutaneous transluminal septal coil embolization for hypertrophic obstructive cardiomyopathy

Steve Ramcharitar, Emanuele Meliga, Sharon W Kirschbaum, Folkert J ten Cate, Robert Jan van Geuns and Patrick W Serruys*

SUMMARY

Background A 48-year-old man with hypertrophic obstructive cardiomyopathy (HOCM) presented with palpitations, symptoms of medically refractory class II angina, and NYHA class II–III heart failure.

Investigations Physical examination revealed a grade 3 systolic murmur that increased to grade 4 with exercise. Echocardiography showed marked septal thickening (17 mm), a left ventricular outflow tract gradient (LVOTG) of 95 mmHg, and a 3+ systolic anterior motion of the mitral valve apparatus. No other pathology was noted with cardiac MRI or with coronary angiography.

Diagnosis Severe symptomatic HOCM.

Management Coil embolization of the first two septal vessels resulted in a limited septal infarct (creatine kinase-MB 36.6 µg/l; troponin T 0.43 µg/l) that corresponded to a mass of 8.1 g on gadolinium contrast cardiac MRI. The LVOTG decreased immediately from 78 mmHg to 35 mmHg. On pressure–volume loops, contractile isovolemic and systolic ejectional parameters decreased, while an improvement in diastolic left ventricular function was observed.

Conclusion Septal coil embolization acutely and effectively reduced the LVOTG in a patient with drug-refractory HOCM.

KEYWORDS coil embolization, hypertrophic obstructive cardiomyopathy, pressure–volume loops

S Ramcharitar is a Clinical Fellow, F ten Cate is Chief of the Echocardiographic Laboratory and PW Serruys is Head of Interventional Cardiology at the Thoraxcenter, Erasmus Medical Center, S Kirschbaum is a Research Fellow in the Department of Cardiology and RJ van Geuns is a Senior Cardiologist at Erasmus Medical Center, Rotterdam, The Netherlands, and E Meliga is an Interventional Cardiologist at San Giovanni Battista Hospital, Turin, Italy.

Correspondence
*Thoraxcenter, Ba 583, Erasmus MC, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands
p.w.j.c.serruys@erasmusmc.nl

Received 31 January 2008 **Accepted** 27 June 2008 **Published online** 7 October 2008
www.nature.com/clinicalpractice
doi:10.1038/ncpcardio1355

THE CASE

A 48-year-old man presented in December 2005 after a syncopal episode whilst exercising in the gym. This was the first time he had experienced syncope and he had no relevant medical history. Holter monitoring was performed and the patient was diagnosed with paroxysmal atrial flutter. He was previously very fit, cycled 30 min daily, and exercised regularly at the gym. He did not smoke or drink alcohol. After his collapse, the patient had progressive chest pains on maximum exertion and felt increasingly lethargic. The patient had five siblings, one of whom had an undiagnosed heart murmur that was never clinically evaluated.

On physical examination, the patient's pulse was regular (70 beats per min [bpm]) and he was normotensive (blood pressure 120/75 mmHg). His heart sounds were normal, but there was a grade 3 systolic ejection crescendo–decrescendo murmur, best heard between the apex and left sternal border, that radiated to the suprasternal notch, but not to the carotid arteries or neck. This murmur increased to grade 4 with the Valsalva maneuver and with isometric exercise (hand-grip), but diminished when the patient squatted down. Electrocardiography revealed sinus rhythm (75 bpm) with poor R-wave progression, early repolarization in precordial leads V1 and V2, and tall R-waves in limb lead II and precordial leads V2 and V3. On an exercise bicycle test, the patient achieved a maximum workload of 140 W and showed a good hemodynamic response (heart rate 176 bpm; blood pressure 213/97 mmHg). He had mild anginal symptoms at maximum exertion, but there were no ischemic changes on electrocardiography. Transthoracic echocardiography (TTE) revealed a hypertrophied interventricular septum, with a maximum end diastolic thickness of 17 mm (anterobasal) and a basal left ventricular outflow tract gradient (LVOTG) of 95 mmHg (flow velocity 4.9 m/s). There was a 3+ systolic anterior motion (SAM) of the mitral valve (see Supplementary Movie online), resulting in an eccentric jet of mild (1+) mitral regurgitation into a dilated left atrium

(diameter 48 mm). On the parasternal long-axis plane, the point of aortal septal attachment was 15 mm below the aortic root. There was noticeable diastolic dysfunction—the mitral valve E to A wave ratio was 1.1 (diastolic dysfunction is defined in our institution as an E to A wave ratio of 0.75–1.5). Left ventricular (LV) diameter and systolic function were both normal. A diagnosis of severe hypertrophic obstructive cardiomyopathy (HOCM) was made on the basis of echocardiography results and the patient was started on metoprolol (75 mg twice daily). Over the next 18 months, despite medical treatment, the patient's palpitations persisted and dyspnea worsened. He was diagnosed with NYHA class II–III heart failure 18 months after presentation and was referred for percutaneous transluminal septal myocardial ablation (PTSMA).

As preparation for PTSMA, the patient underwent coronary angiography, which showed no clinically important coronary artery disease. The right coronary artery was dominant, and from the left anterior descending artery there were two large first septal vessels (Figure 1A). The LV ejection fraction (LVEF) was 70% with a LVOTG of 78 mmHg (Figure 2A). A cardiac MRI scan confirmed local septal hypertrophy with SAM, a normal myocardial mass (143 g), and a good LVEF (77.4%). Delayed, contrast-enhanced MRI using gadolinium diethyl-triaminepentaacetic acid (0.2 mmol/kg intravenously) showed no fibrotic areas (Figure 3A). At 23 months after initial presentation, the patient chose to undergo PTSMA. He was mildly sedated and his left coronary system was cannulated with a Judkins Left 4, 6-French catheter inserted into the right femoral artery through a 6-French sheath. Intravenous heparin (70 IU/kg) was administered to keep the activated clotting time at more than 300 s. As a precaution, a temporary pacing wire was placed in the right ventricle via a 6-French sheath in the right femoral vein and left *in situ* for 48 h after septal coil ablation. The first two septal branches were crossed using Hi-Torque Whisper® (Abbott Vascular, Santa Clara, CA) 0.4 mm guidewires. Contrast TTE—performed by sequentially inflating a 2×8 mm over-the-wire coronary dilatation catheter (Voyager®; Abbott Vascular) proximally at 810.6 kPa (8 atm) and injecting ultrasound contrast media through the lumen—showed opacification of the septal bulge area, indicating that the first two septal perforators were involved.[1] These vessels were coil embolized using a designated microcatheter (Excelsior® SL-10; Boston Scientific, Fremond, CA) to push forward a self-coiling wire 40 mm in length with the 0.4 mm guidewire, which formed a coil with a diameter of 2 mm when the microcatheter was withdrawn. A total of four coils were used, two in each of the septal perforators (Figure 1B). The entire procedure took 75 min to complete, with the first septal perforator treated after 42 min and the second vessel after 64 min.

Online LV pressure–volume measurements were performed following retrograde introduction

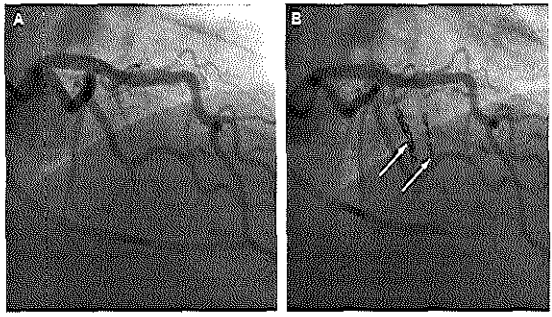


Figure 1 The patient's coronary angiograms. (A) Angiogram taken before coil implantation. (B) Angiogram taken after coil implantation. White arrows show coils in 1st and 2nd septal vessels.

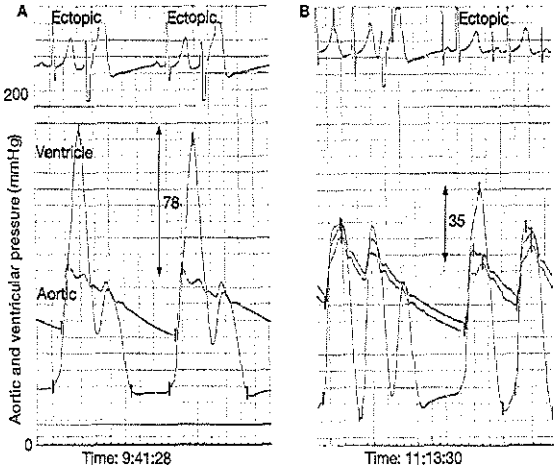


Figure 2 Hemodynamic assessment of left ventricular outflow tract gradient. (A) Assessment before coil implantation. (B) Assessment after coil implantation. The continuous pressure recordings during ectopic heart beats show a decrease (from 78 mmHg to 35 mmHg) immediately after septal coil occlusion.

CASE STUDY

www.nature.com/clinicalpractice/cardio

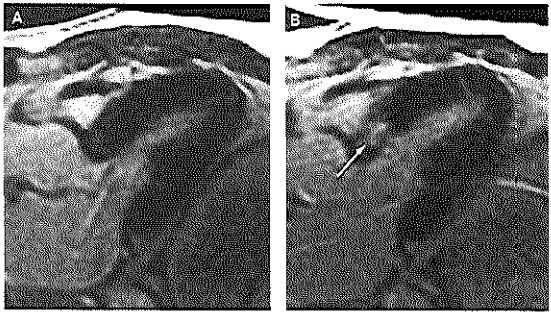


Figure 3 Gadolinium-enhanced MRI scans. **(A)** Scan taken before coil implantation. **(B)** Scan taken 48 h after coil implantation, demonstrating that infarction was confined to the basal anteroseptum (mass 8.1 g; volume 7.7 ml). White arrow shows the infarcted basal septal vessel.

Table 1 Hemodynamic measurements at baseline and after percutaneous transluminal septal coil embolization.

Hemodynamic measurement	Before	After	*P* value
HR (bpm)	75.1±0.33	74.7±0.44	0.08
SW (L×mmHg)	9.9±0.39	9.5±0.27	0.002
SV (ml)	99.3±1.11	93.7±3.3	0.001
CO (l/min)	7.46±0.75	7.01±0.25	<0.001
EF (%)	75.1±0.97	69.9±1.48	<0.001
ESV (ml)	32.8±1.61	40.2±1.71	<0.001
EDV (ml)	132.2±1.78	134±2.54	0.09
ESP (mmHg)	117.1±3.14	119±2.95	0.31
EDP (mmHg)	22.1±1	18.3±1.5	<0.001
dP/dt_{MAX} (mmHg/s)	1455±36	1472±40	0.37
$-dP/dt_{MIN}$ (mmHg/s)	−1541±32	−1826±152	0.001
Tau (m/s)	78.8±3.17	79.7±2.72	0.51
E_{ES} (mmHg/ml)	1.44±0.05	1.42±0.03	0.36
E_{ED} (mmHg/ml)	0.19±0.003	0.16±0.01	<0.001
$V30_{EDPVR}$	138.2±2.1	144±3.42	0.001

Abbreviations: bpm, beats per min; CO, cardiac output; dP/dt_{MAX}, maximum rate of LV pressure change; dP/dt_{MIN}, minimum rate of LV pressure change; EDP, end diastolic pressure; EDPVR, end diastolic pressure–volume relationship; EDV, end diastolic volume; E_{ED}, diastolic stiffness; E_{ES}, end systolic elastance (slope of end systolic pressure–volume relationship) evaluated by single-beat estimation[16]; EF, ejection fraction; ESP, end systolic pressure; ESV, end systolic volume; HR, heart rate; LV, left ventricular; SV, stroke volume; SW, stroke work; Tau, relaxation time constant; $V30_{EDPVR}$, intercept of EDPVR at 30 mmHg (EDPVR assessed by single beat estimation[15]).

of a 7-French combined pressure–conductance catheter (CD Leycom, Zoetermeer, The Netherlands) from the contralateral groin to the LV long axis. The catheter was connected to the CFL-512 cardiac function laboratory (CD Leycom) for acquisition and display of pressure–volume loops. Data analysis was performed offline by custom-made software. Hemodynamics and LV function were assessed by the indexes defined in Table 1. Immediately following septal occlusion, there was a decrease in the continuous LVOTG pressure recordings (from 78 mmHg to 35 mmHg) during ectopic heart beats (Figure 2B). No gradient across the LV outflow tract was recorded during normal R–R intervals. The acute hemodynamic findings observed using pressure–volume loops are summarized in Figure 4 and in Table 1. Peak levels of cardiac enzymes—creatine kinase-MB (36.6 μg/l) and troponin T (0.43 μg/l)—indicated limited infarction. Cardiac MRI performed 48 h after PTSMA demonstrated diminished regional wall thickening in the basal septum and eradication of the SAM. Delayed, contrast-enhanced MRI (Figure 3B) with gadolinium revealed recovery of LV function (LVEF 75.4%) and that the infarct was confined to the basal anteroseptum (mass 8.1 g; volume 7.7 ml).[2] Following routine observation in the coronary care unit for 48 h, the patient had an unremarkable hospital stay and was discharged 4 days after PTSMA on metoprolol 75 mg twice daily. At a clinic visit 1 month after hospital discharge, the patient was asymptomatic and TTE revealed no clinically significant LVOTG; metoprolol was, therefore, discontinued.

DISCUSSION OF DIAGNOSIS

HOCM is an autosomal dominant condition affecting 1 in 500 adults worldwide.[3] The increase in LVOTG seen in patients with HOCM is caused by marked myocardial hypertrophy, particularly of the LV septum, and the associated abnormal SAM of the anterior mitral leaflet. As the obstruction worsens, cardiac output decreases causing fatigue, syncope, dyspnea, angina, arrhythmias, and sudden death.[4] Many of these symptoms were observed in this patient, who first presented with paroxysmal atrial flutter, syncope, and exertional angina. Crucial to the patient's diagnosis of HOCM were echocardiographic findings in accordance with criteria specified in the ACC and European Society of Cardiology guidelines,[5] including a maximum wall thickness of 15 mm or more. HOCM is considered severe if flow velocity is 4 m/s or more with a LVOTG of 50 mmHg or more.[5]

DIFFERENTIAL DIAGNOSIS

The most likely differential diagnosis for the patient's presentation is aortic stenosis, which can

occur at or above the aortic valve. Other possible diagnoses include a globally hypertrophic heart—sometimes seen in athletes and hypertensive patients—or an infiltrative disease, such as amyloidosis. The fact that this patient had asymmetric septal thickening and no subvalvular disease permitted the diagnosis of HOCM.

TREATMENT AND MANAGEMENT

Negative inotropes, such as β-blockers and calcium antagonists, are usually used as first-line treatment of HOCM. In drug-refractory cases, PTSMA (usually with alcohol) and surgical myectomy are alternative therapies.[5] Alcohol septal ablation is associated with relatively low mortality (1–4%), but unpredictable diffusion of alcohol within the myocardial capillary bed can cause high-grade atrioventricular block (in 5–30% of patients).[6] Furthermore, initial stunning of the myocardium can only transiently improve the LVOTG, and ultimate resolution can require several months of septal remodeling.[7] Surgical myectomy offers immediate and permanent abolition of the LVOTG and the opportunity to perform simultaneous mitral valve repair. This procedure does, however, require general anesthesia, carries a mortality of 1–4%, and is associated with a risk of requiring permanent pacemaker implantation, albeit a low one (1%).[5,8] The challenge, therefore, is to find alternative methods for PTSMA that can effectively control the infarct size while improving the outflow gradient.[9,10]

Arterial coil embolization has been successfully used to manage acute bleeds, arterial aneurysms and patent ductus arteriosus.[11] In addition, Durand *et al.* have shown promising results with this technique in 20 drug-refractory patients with HOCM.[12] An average of 3.6 (±1.9) coils were used in each patient, and at 6 months TTE showed that the mean LVOTG had decreased significantly from 80±25 mmHg to 39±28 mmHg ($P=0.001$).[13] No ventricular arrhythmias or permanent atrioventricular blockage were observed. The LVOTG reduction is caused by gradual changes in LV geometry over several weeks or months, which result in an increased cardiac output and a decreased afterload that, together with a reduced LV diastolic pressure, improve diastolic function.[14] General hemodynamics immediately after PTSMA are, however, poorly understood. In this case, the patient's stroke volume, cardiac output and stroke work were significantly reduced immediately after PTSMA. An increase in end systolic volume and the reduction in stroke volume led to a decrease in LVEF and a subsequent acute decline in systolic function. The maximum rate of LV pressure change (dP/dt_{MAX}) did not, however, decline ($P=0.37$). As the above traditional indices can be affected by changes in loading conditions, we also assessed systolic LV function by examining the end systolic pressure–volume relationship. This relatively load-independent relationship showed a rightward shift and a slight decrease in slope after the procedure (Figure 4), indicating a trend towards reduced intrinsic systolic function ($P=0.369$). Conversely, diastolic LV function showed an acute improvement in the minimum rate of LV pressure change (dP/dt_{MIN}). This finding suggests a faster isovolumic relaxation phase in the patient after PTSMA, leading to significantly reduced end diastolic pressure (EDP) and diastolic stiffness (E_{ED}; calculated as EDP divided by

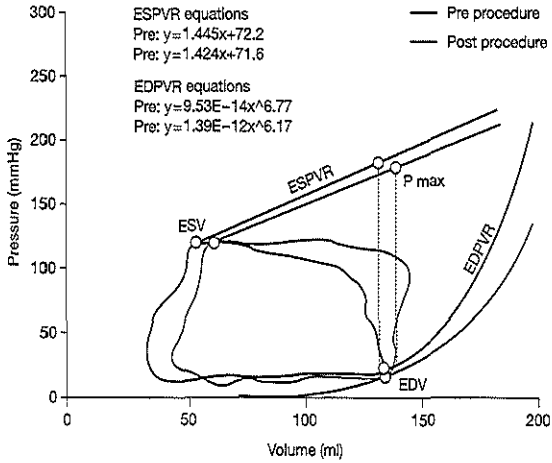


Figure 4 Pressure–volume loops acquired before (black line) and after (red line) coil implantation. The slope of the end systolic pressure–volume relationship (ESPVR) is represented by the equation of the line that includes the end systolic elastance point (superimposable with the end systolic volume [ESV]) and the estimated theoretical maximum pressure point (P max). The change in contractility was determined by the change of the slope of the ESPVR line and its position. The relationship showed a rightward shift and a slight decrease in slope of the ESPVR, indicating a trend towards reducing the intrinsic systolic function. The end diastolic pressure–volume relationship (EDPVR) was estimated using an exponential curve (end diastolic pressure=α×end diastolic volume [EDV]$^{\beta}$). Alpha (α) and beta (β) are obtained by a sequence of calculations from a single set of pressure and volume values, representing the coefficients of the estimated curve. Diastolic left ventricular function showed an acute improvement of the isovolumic relaxation phase (increased minimum rate of left ventricular pressure change) and an improved diastolic compliance (lower end diastolic pressure and decreased α).

CASE STUDY

www.nature.com/clinicalpractice/cardio

Competing interests
The authors declared no competing interests.

end diastolic volume), thus indicating improved diastolic compliance. In line with these findings, the end diastolic pressure–volume relationship (EDPVR) showed a decreased slope as confirmed by the increase in $V30_{EDPVR}$. $V30_{EDPVR}$ is extrapolated from the EDPVR equation, which was obtained according to the single-beat estimation method developed by Klotz *et al.*[15] In our patient, diastolic function was evaluated using several indices, including the minimum rate of LV pressure change, the relaxation time constant, E_{ED}, EDPVR, and $V30_{EDPVR}$. The passive properties of the left ventricle acutely improved immediately after PTSMA—E_{ED} decreased and $V30_{EDPVR}$ increased. These findings are related to the reduction of EDP. In both cases—the increase in $V30_{EDPVR}$ and the decrease in E_{ED}—a decrease in EDP led to results that can be interpreted as an improvement in diastolic function.

CONCLUSIONS

This Case Study illustrates the immediate changes in general hemodynamics, and in systolic and diastolic properties, following septal coil embolization in a patient with drug-refractory HOCM. The acute negative effects of this therapy on pressure–volume hemodynamics are probably due to the important influence that tissue loss has on systolic function in a phase where the compensatory processes have not begun. At 48 h after the procedure, cardiac MRI demonstrated recovery of systolic LVEF in this patient.

Supplementary information in the form of a movie is available on the *Nature Clinical Practice Cardiovascular Medicine* website.

References

1 Pedone C *et al.* (2005) Intracardiac echocardiography guidance during percutaneous transluminal septal myocardial ablation in patients with obstructive hypertrophic cardiomyopathy. *Int J Cardiovasc Intervent* **7:** 134–137
2 O'Hanlon R *et al.* (2007) Use of cardiovascular magnetic resonance for diagnosis and management in hypertrophic cardiomyopathy. *Curr Cardiol Rep* **9:** 51–56
3 Lind JM *et al.* (2006) Genetic basis of hypertrophic cardiomyopathy. *Expert Rev Cardiovasc Ther* **4:** 927–934
4 Maron MS *et al.* (2003) Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* **348:** 295–303
5 Maron BJ *et al.* (2003) American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* **42:** 1687–1713
6 Chen AA *et al.* (2006) Acute predictors of subacute complete heart block after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Am J Cardiol* **97:** 264–269
7 van Dockum WG *et al.* (2005) Early onset and progression of left ventricular remodeling after alcohol septal ablation in hypertrophic obstructive cardiomyopathy. *Circulation* **111:** 2503–2508
8 van der Lee C *et al.* (2005) Percutaneous versus surgical treatment for patients with hypertrophic obstructive cardiomyopathy and enlarged anterior mitral valve leaflets. *Circulation* **112:** 482–488
9 Oto A *et al.* (2007) New approach to septal ablation: glue (cyanoacrylate) septal ablation. *Catheter Cardiovasc Interv* **69:** 1021–1025
10 Sianos G *et al.* (2006) Hypertrophic obstructive cardiomyopathy: septal ablation with overlapping sirolimus-eluting and covered stents after failed alcoholization and concomitant coronary artery disease. *Circulation* **114:** e553–e555
11 Kereiakes DJ *et al.* (2006) Coil embolization of a circumflex coronary aneurysm at the time of percutaneous coronary stenting. *Catheter Cardiovasc Interv* **67:** 607–610
12 Durand E *et al.* (2006) Percutaneous transluminal septal coil embolization for hypertrophic obstructive cardiomyopathy [abstract #3598]. *Circulation* **114:** II_768
13 Durand E *et al.* (2008) Non-surgical septal myocardial reduction by coil embolization for hypertrophic obstructive cardiomyopathy: early and 6 months follow-up. *Eur Heart J* **29:** 348–355
14 Sitges M *et al.* (2003) Comparison of left ventricular diastolic function in obstructive hypertrophic cardiomyopathy in patients undergoing percutaneous septal alcohol ablation versus surgical myotomy/myectomy. *Am J Cardiol* **91:** 817–821
15 Klotz S *et al.* (2006) Single-beat estimation of end-diastolic pressure-volume relationship: a novel method with potential for noninvasive application. *Am J Physiol Heart Circ Physiol* **291:** H403–H412
16 Takeuchi M *et al.* (1991) Single-beat estimation of the slope of the end-systolic pressure-volume relation in the human left ventricle. *Circulation* **83:** 202–212

PART 5

CELL TRANSPLANTATION

CHAPTER 20

ADIPOSE-DERIVED CELLS

REVIEW

Adipose-Derived Cells

Emanuele Meliga,* Brian M. Strem,† H. J. Duckers,* and Patrick W. Serruys*

*Thoraxcenter, Erasmus University Medical Center Rotterdam, 3000 CA Rotterdam, The Netherlands
†Cytori Therapeutics, Inc., San Diego, CA 92121, USA

Heart failure is by far the most common cause of hospitalization in Western countries, with onerous economic consequences. Cell therapy holds great promise for use in tissue regeneration and is increasingly used in an effort to improve outcomes in cardiac disease. Recently it has been shown that adipose tissue, in addition to committed adipogenic, endothelial progenitor cells and pluripotent vascular progenitor cells, also contains multipotent cell types (adipose-derived stem cells, ADSCs) that, in cell culture conditions, have shown to have an impressive developmental plasticity including the ability to undergo multilineage differentiation and self-renewal. ADSCs express multiple CD marker antigens similar to those observed on MSCs and are also capable of secreting a large number of angiogenesis-related cytokines, including vascular endothelial growth factor, granulocyte/macrophage colony stimulating factor, stromal-derived factor-1α, and hepatocyte growth factor. Adipose tissue can be harvested in large quantities with minimal morbidity in several regions of the body and, on average, 100 ml of human adipose tissue yields about 1×10^6 stem cells. Studies conducted in porcine AMI models have shown a significant LV functional improvement, with no report of any potentially fatal arrhythmias. The APOLLO trial, a prospective, double blind, randomized, placebo-controlled trial currently in the recruiting phase, is a "first-in-man" study that explores the safety and feasibility of ADSC transplantation in patients with acute MI.

Key words: Cardiac regeneration; Adipose-derived stem cells; Heart failure; Acute myocardial infarction

INTRODUCTION

Primary PCI, thanks to enormous improvements in materials and devices, is nowadays considered the gold standard for the treatment of AMI and leads to excellent safety and efficacy results. Nevertheless, revascularization therapies, though able to restore perfusion and contractile function of postinfarct stunned or hibernated myocardium, have no effect on necrotic tissue.

Postinfarction myocardial necrosis and subsequent formation of fibrotic scar that replaces viable myocardium leads to depressed systolic function, reduced diastolic compliance, left ventricular remodeling, and ultimately to congestive heart failure progression, by far the most common cause of hospitalization in Western countries, with onerous economic consequences.

The potential of cell transplantation to repair damaged myocardium and to grow new viable tissue is attractive, and has been widely studied in both experimental and clinical conditions using various cell types (8–10,24,35,42).

The characteristics of the ideal cell still remain to be defined, but it appears clear that, among the cells efficient in the treatment of heart disease, cells that are autologous, nonembryonic, do not require culturing to obtain a therapeutic dose, and can be administered during the same procedure may be logistically easier to use.

Mesenchymal stem cells, referred also to as marrow stromal cells (MSCs), have shown to have some of the above-mentioned ideal properties; MSCs in fact are multipotent adult stem cells that can expand in culture and are able to differentiate into multiple mesenchymal cell phenotypes, including bone, cartilage, and fat. In addition, MSCs are capable of nonmesenchymal phenotypic differentiation into neurons, skeletal muscle progenitor cells, vascular endothelial cells, and cardiomyocytes (14,20,22,31,40,53,55).

So far, these cells have been harvested from bone

Address correspondence to Prof. P. W. Serruys, M.D., Ph.D., Director of the Interventional Cardiology Department, Thoraxcenter, Erasmus MC, Erasmus University, Dr Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands. Tel: 0031104635260; E-mail: p.w.j.c.serruys@erasmusmc.nl

marrow, a tissue source that presents multiple limitations, including: a) donor site morbidity limits the amount of marrow that can be obtained (generally 40–50 ml) (3,18); b) MSCs represent <0.01% of all nucleated bone marrow cells in healthy volunteers (approximately 1 in 25,000 to 1 in 100,000) (4,5); and c) requires extended time in culture to obtain therapeutic cell doses by ex vivo cell expansion, rendering treatment in the acute phase of myocardial infarction impractical.

Recently it has been shown that adipose tissue, in addition to committed adipogenic, endothelial progenitor cells and pluripotent vascular progenitor cells, contains multipotent cells, similar to MSCs (58,59). This finding has generated major interest because, in contrast to bone marrow, large quantities of adipose tissue can be easily and safely harvested with minimal morbidity, making it an appealing source for cell therapy.

CELL CHARACTERISTICS

Adipose tissue has a notable plasticity during life. Although cellular hypertrophy can partially enable increases in volume, large variations are usually associated with an increase in adipocyte count (cellular hyperplasia) accompanied by a concomitant expansion and remodeling of the microvasculature supplying these cells (1).

The hyperplastic process of the adipose tissue was formerly thought to be mediated by a population of unipotent progenitor cells called preadipocytes. These cells have been demonstrated to have potential beyond that of the adipocytic lineage, with an impressive developmental plasticity (23,58), including the ability to undergo multilineage differentiation and self-renewal (49, 54,57,59) (Fig. 1). These cells, present within the stromal vascular fraction of adipose tissue, are generally referred to as adipose-derived stem cells (ADSCs).ADSCs are a cell population with properties that are very similar, though not identical, to those of marrow-derived MSCs (7,38,39,52).

These cells have extensive proliferative capacity and are able to undergo differentiation along both mesenchymal lineages (adipogenesis, chondrogenesis, osteogenesis) (11,14,20,22,31,40,53,55) and nonmesenchymal lineages (endothelial, smooth muscle and neurogenic), confirming the transdifferentiation ability of ADSCs (40,41).

In culture, these cells have a surface phenotype rather similar to the MSC phenotype (Table 1): both cell types express CD117 (stem cell factor receptor), CD105, STRO1, and CD166 (multilineage differentiation markers) (6,19,26,43), CD90, CD54 (ICAM-1), CD44 and CD29 (β1-integrin) (13,14), whereas both cell types do not express the endothelial markers CD31, CD34, and the hematopoietic marker CD45 (7,19).

However, MSCs and ADSCs have a number of relatively slight distinctions, the most interesting of which is the reciprocal expression pattern of the very-late-activation antigen 4 or VLA-4 (CD49d/CD29) and its cognate receptor vascular cell-adhesion molecule 1 or VCAM-1 (CD106). ADSCs express VLA-4 but not VCAM-1 in the majority of donors, while MSCs usually express VCAM-1 and not VLA-4 (7).

The consequences of these properties are not clear yet, but this observation is fascinating because both these molecules play an important role in the homing and mobilization process of hematopoietic stem cell from bone marrow (44,48).

MSCs and ADSCs are also known to secrete a large number of angiogenesis-related cytokines (37). ADSCs in standard cultures secrete high levels of hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), placental growth factor (PlGF), transforming growth factor-β (TGF-β), fibroblast growth factor (FGF), granulocyte/macrophage colony stimulating factor (GM-CSF), monocyte chemotactic protein-1 (MCP-1), and stromal-derived factor-1α (SDF-1α), suggesting an important role of ADSCs in neovascularization (36,37).

Clonally derived, multipotent cells from adipose tissue display an immunoprivileged behavior (39). Less than 1% of ADSCs express the cell surface MHC class-I, while class-II is almost absent (25), being therefore poorly recognized by T lymphocytes. Moreover, ADSCs have the ability to suppress lymphocyte reaction in a dose- and time-dependent fashion; such immunosuppression probably occurs via the production of IL-4, IL-10, and TGF-β, responsible for the inhibition of lymphocyte proliferation (34).

These characteristics, together with the easy availability and the small amount of tissue needed for their isolation, suggest that ADSCs might even have potential as immunoprivileged universal donor cells with the prospective possibility to be used also for allogenic transplantation.

Large quantities of subcutaneous adipose tissue can be safely harvested using liposuction in several regions of the body. A typical harvest out of 100–200 ml of human adipose tissue contains about 5×10^7 nucleated cells. After enzymatic digestion, filtration, and centrifugation processes, the nonbuoyant stromal cells part from the buoyant adipocytes (29,32,33). The nonbuoyant fraction can yield in excess of 1×10^6 stem cells (from 100 cc of fat tissue), about 45-fold more than a typical harvest of bone marrow aspiration (of 40 ml), which normally contains 2.5×10^4 MSCs in a mature adult (3,30). The ADSC-containing fraction can be cultured with different media (e.g., DMEM-F12; EGM-2-MV, α-MEM, etc.) and supplemented with different growth factors (e.g., VEGF, insulin-like growth factor, basic FGF, etc.)

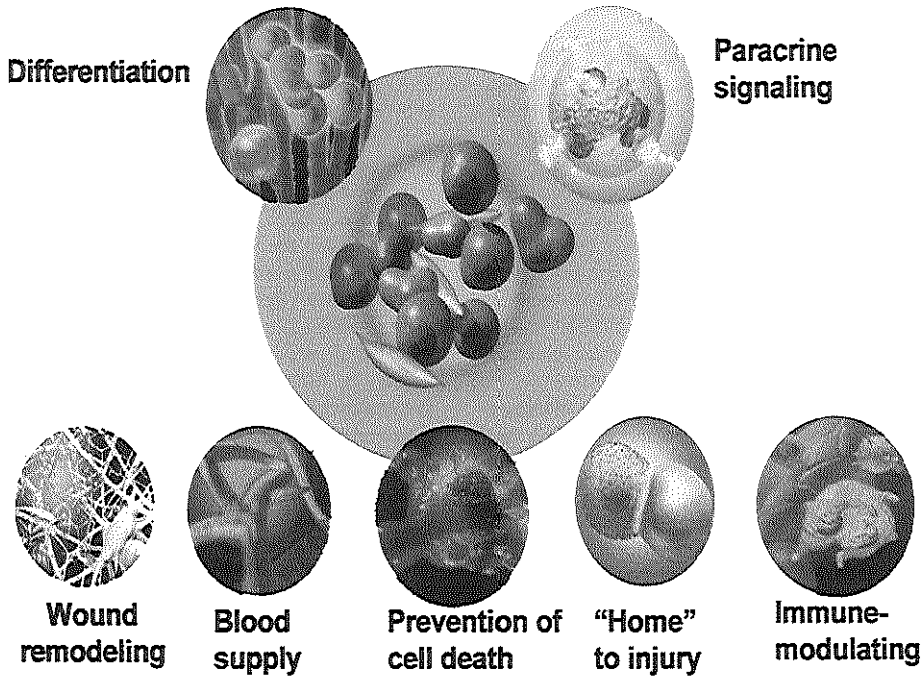


Figure 1. Multiple mechanisms of cell regeneration enacted by ADSCs.

to stimulate expansion and differentiation into dedicated lineages. Due to the great concentration of ADSCs normally present in an adipose tissue harvest, it is also possible to obtain therapeutic cell doses in as little as 1 after liposuction, without further expansion in culture (32,33), therefore avoiding cell alterations often associated with culturing.

Table 1. Cell Surface Characteristics of Adipose-Derived Stem Cells and Mesenchymal Stem Cells

Cell Surface Marker	ADSCs	MSCs
CD29	+	+
CD44	+	+
CD54	+	+
CD90	+	+
CD105	+	+
CD166	+	+
STRO-1	+	+
CD31	−	−
CD34	−	−
CD45	−	−
CD49D	+	−
CD106	−	+

DIFFERENTIATION CAPABILITIES OF ADSCs

ADSCs, similarly to MSCs, have the ability to undergo differentiation along both mesenchymal (fat, bone, cartilage) and nonmesenchymal lineages (endothelial cells, smooth muscle) (13,15,20,22,44,45), demonstrating that adipose tissue contains pluripotent cells. Furthermore, concerning muscle differentiation, evidence shows that ADSCs have the capability to differentiate into contractile cells with either striated muscle cells or cardiomyocyte features (12,21,27,50,56).

In Vitro Studies of ADSC Differentiation

After isolation and expansion of processed lipoaspirate (PLA) clones, PLA cells expressed multiple CD marker antigens similar to those observed on MSCs, as observed by Zuk et al. in 2002 (58). During in vitro culture with various supplementation, PLA clones differentiated into different mesodermal lineages (examined lineages were: osteogenic, chondrogenic, adipogenic), while some clones exhibited differentiation potential into all of these lineages. These trilineage clones were designated as ADSCs, confirming therefore the presence of a stem cell population within adipose tissue. In addition to mesodermal lineages, PLA cells

and clones showed the capability to differentiate into putative neurogenic cells, exhibiting morphology and a protein pattern consistent with the neuronal phenotype.

In 2005, Planat-Benard et al. (32) obtained extraordinary results by plating fresh ADSCs in a semisolid culture. After 3 weeks of culture, ADSCs morphologically developed into ventricle-like, atrial-like, and pacemaker-like cells, displaying tight intercellular connections (evidenced by Cx-43) and spontaneous as well as triggered action potentials with beating. Moreover, these differentiated cells expressed the cardiac-specific transcription factors Nkx2.5, GATA-4, and MEF-2C, the structural cardiac proteins β-myosin heavy chain (MHC), myosin light chain-2 ventricular (MLC-2v), myosin light chain-2 atrial (MLC-2a) as well as the atrial natriuretic peptide (ANP), whereas the skeletal marker MyoD and smooth muscle actin were not expressed. Consistent with these results, after 3 weeks of exposure of ADSCs with a permeable cell membrane to rat cardiomyocyte extracts, the ADSCs expressed cardiomyocyte markers including sarcomeric alpha-actin, desmin, and cardiac troponin I, as well as the gap junction protein connexin-43 (Cx-43) and started to beat spontaneously, as observed by Gaustad et al. in 2004 (17).

In Vivo Studies of ADSC Differentiation

Several groups have so far reported data about the safety and efficacy of ADSCs to regenerate damaged myocardium in both small (rats) and large animals (pigs). Strem and colleagues (46) in 2005 used intraventricular injections to deliver freshly isolated ADSCs from Rosa 26 mice (expressing the β-galactosidase transgene) into syngeneic recipient mice, following myocardial cryoinjury. β-Galactosidase-positive cells were found in treated mice together with the expression of MHC, Nkx2.5, and troponin I at 14 days posttransplantation, suggesting that ADSCs have the ability to engraft injured myocardium and express specific cardiomyocyte markers in vivo.

In another study conducted by the same group, syngeneic freshly isolated ADSCs were injected into the LV chamber of 10 female Lewis rats after 60-min occlusion of the LAD, resulting in significant increases of 5.1% and 7.7% delta in LVEF at 4 and 12 weeks (Fig. 2), respectively, compared with control rats (saline treated, $n = 10$). This study also demonstrated significant improvements in both dP/dt_{max} and dP/dt_{min} in the ADSC-treated rats compared to controls (Table 2) (47). Moreover, in accordance with the previous study, cell engraftment was demonstrated 7 days after transplantation (Fig. 3).

Delivery of ADSCs by intracoronary infusion into pigs 2 days after an acute MI through a LAD balloon occlusion resulted in a 3% absolute increase in LVEF while the untreated pigs showed a 9% decline at 6-month follow-up ($p < 0.01$) (51). Likewise, intracoronary infusion of either ADSCs or MSCs in an acute MI pig model resulted in an 11.4% improvement of absolute LVEF after 4 weeks, compared to only 2% improvement in the nontreated group ($p < 0.003$) (50).

Freshly isolated ADSCs given immediately after reperfusion in a porcine AMI model resulted in a 8% LVEF increase compared to controls at 8-week follow-up ($p = 0.023$) (2).

Interestingly, concordant with the functional improvement, wall thickness and capillary density were both significantly increased in the border infarct areas of the treated group, compared to the control group (28).

In a study recently published by Miyahara and colleagues (29), ADSCs were transplanted directly onto infarcted murine hearts as a monolayered cell sheet. After transplantation, the engrafted sheet gradually grew to form a thick stratum that included newly formed vessels, undifferentiated cells, and cardiomyocytes. Autologous transplantation of ADSC sheets resulted in a decreased LVEDP, improved maximum and minimum dP/dt, increased diastolic wall thickness, increased left ventricular fractional shortening, and decreased diastolic wall stress, compared to dermal fibroblast sheets taken as a control.

Human Studies of ADSC Differentiation

ADSCs have been used successfully in a variety of indications in humans, including bone reconstruction, the treatment of Crohn's disease fistulas (15,16), osteogenesis imperfecta (21), and for breast augmentation and reconstruction after partial mastectomy (56). The APOLLO trial, currently recruiting patients, is the "first-in-man" study that explores the safety and feasibility of ADSC transplantation in patients with acute MI. The APOLLO trial is a prospective, double blind, randomized, placebo-controlled, sequential dose escalation study that will enroll up to 48 patients (4 cohorts of 12 patients each) with acute MI at the Thoraxcenter, Erasmus MC, Rotterdam.

Eligible patients are enrolled following primary PCI and undergo liposuction and isolation of the adipose-derived regenerative cells fraction (ADRCs) using the Celution™ system (Fig. 4). ADRCs are then injected within 24 h from the primary PCI into the culprit coronary artery.

Main safety end points include: major adverse cardiac or cerebral event (MACCE) rates, serious adverse events (SAEs)/adverse events (AEs) rates and a composite clinical end point of death, MI, stroke, and rehospitalization for heart failure. Main feasibility end points are: absolute LVEF and changes in LVEF from baseline to 6 months, MI size, regional wall thickness and thickening in all segments, LV end systolic volume (LV-

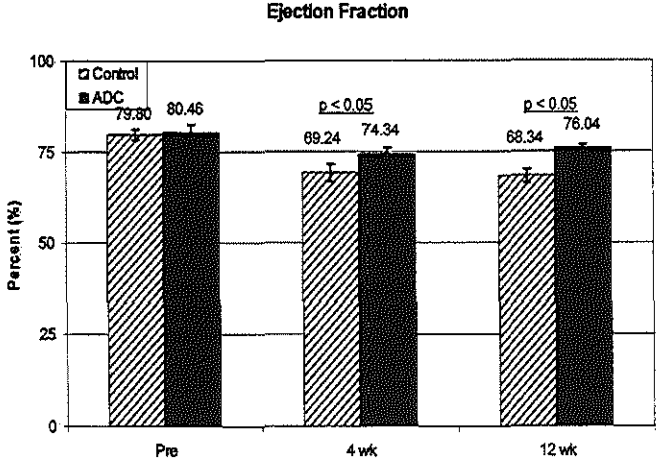


Figure 2. LVEF evaluated by echocardiography at 4 and 12 weeks showed a significant improvement in the group treated with ACSCs (ADC) compared to the control group (Control).

ESV), LV end diastolic volume (LV-EDV), and change in perfusion defect after revascularization to 6 months as measured by contrast enhanced MRI, echocardiography, and scintigraphy.

Patients will be followed for 36 months and will undergo imaging studies (2D/3D echocardiography, LV angiography, MRI, SPECT), functional evaluation (left ventricular pressure–volume relationship), clinical evaluations, and laboratory testing at 6, 12, and 18 months.

SIDE EFFECTS, ADVERSE EVENTS AND POTENTIAL HURDLES

The main issue related to transplanted cells is their potential arrhythmogenicity. Previous reports conducted using skeletal myoblasts showed an increased rate of arrhythmic events in the treated groups that raised important interrogatives on the safety of this treatment and that led often to prophylactic AICD implantation (27).

Although limited safety data are available to date, in vivo preliminary animal studies conducted using ADSCs have not reported an increase in any potentially fatal arrhythmias. For instance, loop recorder monitoring in pigs treated with ADRCs (12) did not show an increase in fatal arrhythmic events or sustained arrhythmias (e.g., bradycardia lower than 45/min or tachycardia above 165/min) in the treated animals. Programmed right ventricular stimulation did not show an increase in susceptibility for arrhythmias by ADRC treatment. On the contrary, cycle length was significantly longer in the ADRC group at the beginning of an induced arrhythmia, suggesting rather a reduction in the overall inducibility of malignant arrhythmias than an increase in susceptibility. In addition, there have been no reports on arrhythmias in patients who underwent intramyocardial injections of ADRCs using the NOGA delivery system in patients with chronic myocardial ishemia in the PRECISE trial.

Issues associated with tissue harvest in patients with a recent AMI under high doses of anticoagulants, GP IIb-IIIa inhibitors, and aspirin are a potential concern, owing to the highly developed vascularization of adipose tissue and the consequent bleeding risk. However, only a relatively small amount of tissue is required to obtain an effective cell dose, and hemostasis at the site of liposuction can easily be achieved by local pressure.

Table 2. dP/dt Evaluated at 12 Weeks by Millar Pressure Tip Catheter Is Significantly Higher in the Group Treated With ADSCs Compared to the Control Group (Saline Treated)

	Saline Treated	ADC Treated	*p*-Value
+dP/dt	2837.61 (301.19)	5494.46 (550.76)	0.015
−dP/dt	−2716.49 (331.83)	−6323.28 (544.61)	0.003

Values are mmHg/s with SE in parentheses.

CONCLUSIONS

Human adipose tissue is an interesting source of multipotent stem cells that have the ability to differentiate into several mesenchymal and nonmesenchymal lineages (including vascular and cardiomyocytes lineages), demonstrate stem cell-like extensive self-renewal, and secrete several factors with angiogenic and antiapoptotic effects. Moreover, ADSCs/ADRCs, unlike bone mar-

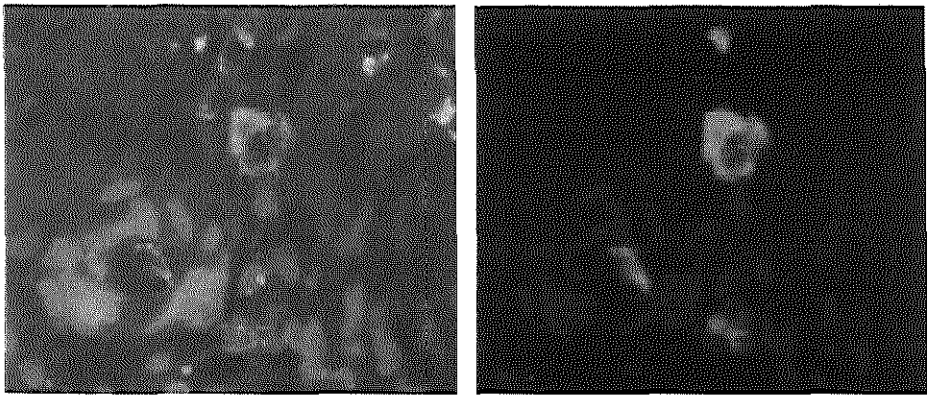


Figure 3. Histologic samples taken at day 7 posttransplantation in the AMI broder region of ADC-treated rats showing ADSC engraftment. Left: green channel on. Right: green channel off. Red = anti-GFP immunostaining, blue = DAPI.

row-derived MSCs, can be easily and safely obtained in large numbers, without the necessity to culture and expand them to obtain a therapeutic dose.

ADRCs have already been used in humans in different clinical settings with excellent results and few side effects. Preclinical studies conducted in animal AMI models showed that ADSCs have the capability to differentiate into cardiac muscle cells as well as to excrete different growth factors with important proangiogenic effects that led to a significant improvement of ejection fraction and wall thickness.

The APOLLO trial, a "first-in-men" study conducted with ADSCs in AMI patients, will provide fundamental data about the safety and efficacy of these cells in humans, providing an essential insight on what could be their role in the treatment of cardiovascular disease.

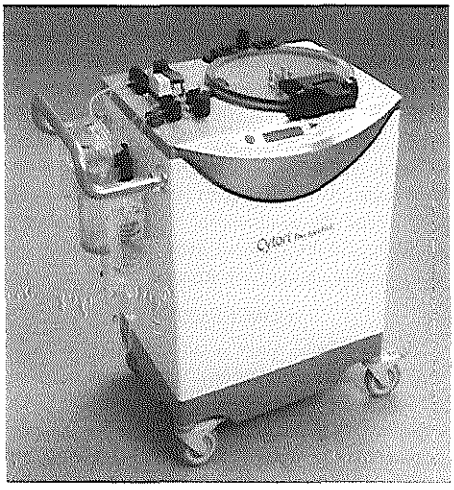


Figure 4. The Celution™ system. Reproduced with permission

REFERENCES

1. Ailhaud, G.; Grimaldi, P.; Negrel, R. Cellular and molecular aspects of adipose tissue development. Annu. Rev. Nutr. 12:207–233; 1992.
2. Alt, E.; Scharlau, M.; Pinkernell, K.; Amadi, C.; Reddy, K.; Matthias, N.; Daemen, K.; Fotuhi, P. Uncultured, autologous adipose-derived stromal cells—a novel cell source for cardiac repair. Am. J. Cardiol. 96(7):71–72; 2005.
3. Bacigalupo, A.; Tong, J.; Podesta, M.; Piaggio, G.; Figari, O.; Colombo, P.; Sogno, G.; Tedone, E.; Moro, F.; Van Lint, M. T. Bone marrow harvest for marrow transplantation: Effect of multiple small (2 ml) or large (20 ml) aspirates. Bone Marrow Transplant. 9(6):467–470; 1992.
4. Banfi, A.; Bianchi, G.; Galotto, M.; Cancedda, R.; Quarto, R. Bone marrow stromal damage after chemo/radiotherapy: Occurrence, consequences and possibilities of treatment. Leuk. Lymphoma 42(5):863–870; 2001.
5. Banfi, A.; Podesta, M.; Fazzuoli, L.; Sertoli, M. R.; Venturini, M.; Santini, G.; Cancedda, R.; Quarto, R. High-dose chemotherapy shows a dose-dependent toxicity to bone marrow osteoprogenitors: A mechanism for post-bone marrow transplantation osteopenia. Cancer 92(9): 2419–2428; 2001.
6. Dennis, J. E.; Carbillet, J. P.; Caplan, A. I.; Charbord, P. The STRO-1+ marrow cell population is multipotential. Cells Tissues Organs 170(2–3):73–82; 2002.
7. De Ugarte, D. A.; Alfonso, Z.; Zuk, P. A.; Elbarbary, A.; Zhu, M.; Ashjian, P.; Benhaim, P.; Hedrick, M. H.; Fraser, J. K. Differential expression of stem cell mobilization-associated molecules on multi-lineage cells from adipose tissue and bone marrow. Immunol. Lett. 89(2–3):267–270; 2003.
8. Dimmeler, S.; Zeiher, A. M. Wanted! The best cell for cardiac regeneration. J. Am. Coll. Cardiol. 44(2):464–466; 2004.

my heart: The scientific foundations of cardiac repair. J. Clin. Invest. 115(3):572–583; 2005.
10. Edelberg, J. M.; Xaymardan, M.; Rafii, S.; Hong, M. K. Adult cardiac stem cells—where do we go from here? Sci. Aging Knowledge Environ. 2003(26):PE17; 2003.
11. Erickson, G. R.; Gimble, J. M.; Franklin, D. M.; Rice, H. E.; Awad, H.; Guilak, F. Chondrogenic potential of adipose tissue-derived stromal cells in vitro and in vivo. Biochem. Biophys. Res. Commun. 290(2):763–769; 2002.
12. Fotuhi, P.; Scharlau, M.; Matthias, N.; Pinkernell, K.; Ferguson, B.; Alt, E. Effects of intracoronary adipose tissue derived stem cell transplantation on sudden cardiac death and fibrillation cycle length in pigs with myocardial infarction. Clin. Res. Cardiol. 6(95):167–169; 2006.
13. Fraser, J. K.; Schreiber, R.; Strem, B.; Zhu, M.; Alfonso, Z.; Wulur, I.; Hedrick, M. H. Plasticity of human adipose stem cells toward endothelial cells and cardiomyocytes. Nat. Clin. Pract. Cardiovasc. Med. 3(Suppl. 1):S33–37; 2006.
14. Fraser, J. K.; Wulur, I.; Alfonso, Z.; Hedrick, M. H. Fat tissue: An underappreciated source of stem cells for biotechnology. Trends Biotechnol. 24(4):150–154; 2006.
15. Garcia-Olmo, D.; Garcia-Arranz, M.; Garcia, L. G.; Cuellar, E. S.; Blanco, I. F.; Prianes, L. A.; Montes, J. A.; Pinto, F. L.; Marcos, D. H.; Garcia-Sancho, L. Autologous stem cell transplantation for treatment of rectovaginal fistula in perianal Crohn's disease: A new cell-based therapy. Int. J. Colorectal Dis. 18(5):451–454; 2003.
16. Garcia-Olmo, D.; Garcia-Arranz, M.; Herreros, D.; Pascual, I.; Peiro, C.; Rodriguez-Montes, J. A. A phase I clinical trial of the treatment of Crohn's fistula by adipose mesenchymal stem cell transplantation. Dis. Colon Rectum 48(7):1416–1423; 2005.
17. Gaustad, K. G.; Boquest, A. C.; Anderson, B. E.; Gerdes, A. M.; Collas, P. Differentiation of human adipose tissue stem cells using extracts of rat cardiomyocytes. Biochem. Biophys. Res. Commun. 314(2):420–427; 2004.
18. Gluckman, E.; Horowitz, M. M.; Champlin, R. E.; Hows, J. M.; Bacigalupo, A.; Biggs, J. C.; Camitta, B. M.; Gale, R. P.; Gordon-Smith, E. C.; Marmont, A. M. Bone marrow transplantation for severe aplastic anemia: Influence of conditioning and graft-versus-host disease prophylaxis regimens on outcome. Blood 79(1):269–275; 1992.
19. Gronthos, S.; Franklin, D. M.; Leddy, H. A.; Robey, P. G.; Storms, R. W.; Gimble, J. M. Surface protein characterization of human adipose tissue-derived stromal cells. J. Cell Physiol. 189(1):54–63; 2001.
20. Halvorsen, Y. D.; Franklin, D.; Bond, A. L.; Hitt, D. C.; Auchter, C.; Boskey, A. L.; Paschalis, E. P.; Wilkison, W. O.; Gimble, J. M. Extracellular matrix mineralization and osteoblast gene expression by human adipose tissue-derived stromal cells. Tissue Eng. 7(6):729–741; 2001.
21. Horwitz, E. M.; Gordon, P. L.; Koo, W. K.; Marx, J. C.; Neel, M. D.; McNall, R. Y.; Muul, L.; Hofmann, T. Isolated allogeneic bone marrow-derived mesenchymal cells engraft and stimulate growth in children with osteogenesis imperfecta: Implications for cell therapy of bone. Proc. Natl. Acad. Sci. USA 99:8932–8937; 2002.
22. Jiang, Y.; Jahagirdar, B. N.; Reinhardt, R. L.; Schwartz, R. E.; Keene, C. D.; Ortiz-Gonzalez, X. R.; Reyes, M.; Lenvik, T.; Lund, T.; Blackstad, M.; Du, J.; Aldrich, S.; Lisberg, A.; Low, W. C.; Largaespada, D. A.; Verfaillie, C. M. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature 418(6893):41–49; 2002.
23. Katz, A. J.; Tholpady, A.; Tholpady, S. S.; Shang, H.; tion of human adipose-derived adherent stromal (hADAS) cells. Stem Cells 23(3):412–423; 2005.
24. Laflamme, M. A.; Murry, C. E. Regenerating the heart. Nat. Biotechnol. 23(7):845–856; 2005.
25. Lee, R. H.; Kim, B.; Choi, I.; Kim, H.; Choi, H. S.; Suh, K.; Bae, Y. C.; Jung, J. S. Characterization and expression analysis of mesenchymal stem cells from human bone marrow and adipose tissue. Cell Physiol. Biochem. 14(4–6):311–324; 2004.
26. Majumdar, M. K.; Thiede, M. A.; Mosca, J. D.; Moorman, M.; Gerson, S. L. Phenotypic and functional comparison of cultures of marrow-derived mesenchymal stem cells (MSCs) and stromal cells. J. Cell Physiol. 176(1):57–66; 1998.
27. Makkar, R. R.; Lill, M.; Chen, P. S. Stem cell therapy for myocardial repair: Is it arrhythmogenic? J. Am. Coll. Cardiol. 42(12):2070–2072; 2003.
28. Matthias, N.; Schwarzer, M.; Pinkernell, K.; Fotuhi, P.; Alt, E. U. Effect of stem cells on left ventricular wall thickness and capillary density in pigs following myocardial infarction. J. Am. Coll. Cardiol. 47(4):206–207; 2006.
29. Miyahara, Y.; Nagaya, N.; Kataoka, M.; Yanagawa, B.; Tanaka, K.; Hao, H.; Ishino, K.; Ishida, H.; Shimizu, T.; Kangawa, K.; Sano, S.; Okano, T.; Kitamura, S.; Mori, H. Monolayered mesenchymal stem cells repair scarred myocardium after myocardial infarction. Nat. Med. 12(4): 459–465; 2006.
30. Muschler, G. F.; Nitto, H.; Boehm, C. A.; Easley, K. A. Age- and gender-related changes in the cellularity of human bone marrow and the prevalence of osteoblastic progenitors. J. Orthop. Res. 19(1):117–125; 2001.
31. Nagaya, N.; Kangawa, K.; Itoh, T.; Iwase, T.; Murakami, S.; Miyahara, Y.; Fujii, T.; Uematsu, M.; Ohgushi, H.; Yamagishi, M.; Tokudome, T.; Mori, H.; Miyatake, K.; Kitamura, S. Transplantation of mesenchymal stem cells improves cardiac function in a rat model of dilated cardiomyopathy. Circulation 112(8):1128–1135; 2005.
32. Planat-Benard, V.; Menard, C.; Andre, M.; Puceat, M.; Perez, A.; Garcia-Verdugo, J. M.; Penicaud, L.; Casteilla, L. Spontaneous cardiomyocyte differentiation from adipose tissue stroma cells. Circ. Res. 94(2):223–229; 2004.
33. Planat-Benard, V.; Silvestre, J. S.; Cousin, B.; Andre, M.; Nibbelink, M.; Tamarat, R.; Clergue, M.; Manneville, C.; Saillan-Barreau, C.; Duriez, M.; Tedgui, A.; Levy, B.; Penicaud, L.; Casteilla, L. Plasticity of human adipose lineage cells toward endothelial cells: Physiological and therapeutic perspectives. Circulation 109(5):656–663; 2004.
34. Puissant, B.; Barreau, C.; Bourin, P.; Clavel, C.; Corre, J.; Bousquet, C.; Taureau, C.; Cousin, B.; Abbal, M.; Laharrague, P.; Penicaud, L.; Casteilla, L.; Blancher, A. Immunomodulatory effect of human adipose tissue-derived adult stem cells: Comparison with bone marrow mesenchymal stem cells. Br. J. Haematol. 129(1):118–129; 2005.
35. Rafii, S.; Lyden, D. Therapeutic stem and progenitor cell transplantation for organ vascularization and regeneration. Nat. Med. 9(6):702–712; 2003.
36. Rehman, J.; Considine, R. V.; Bovenkerk, J. E.; Li, J.; Slavens, C. A.; Jones, R. M.; March, K. L. Obesity is associated with increased levels of circulating hepatocyte growth factor. J. Am. Coll. Cardiol. 41(8):1408–1413; 2003.
37. Rehman, J.; Traktuev, D.; Li, J.; Merfeld-Clauss, S.; Temm-Grove, C. J.; Bovenkerk, J. E.; Pell, C. L.; John-

of angiogenic and antiapoptotic factors by human adipose stromal cells. Circulation 109(10):1292–1298; 2004.
38. Rodriguez, A. M.; Elabd, C.; Amri, E. Z.; Ailhaud, G.; Dani, C. The human adipose tissue is a source of multipotent stem cells. Biochimie 87(1):125–128; 2005.
39. Rodriguez, A. M.; Pisani, D.; Dechesne, C. A.; Turc-Carel, C.; Kurzenne, J. Y.; Wdziekonski, B.; Villageois, A.; Bagnis, C.; Breittmayer, J. P.; Groux, H.; Ailhaud, G.; Dani, C. Transplantation of a multipotent cell population from human adipose tissue induces dystrophin expression in the immunocompetent mdx mouse. J. Exp. Med. 201(9):1397–1405; 2005.
40. Safford, K. M.; Hicok, K. C.; Safford, S. D.; Halvorsen, Y. D.; Wilkison, W. O.; Gimble, J. M.; Rice, H. E. Neurogenic differentiation of murine and human adipose-derived stromal cells. Biochem. Biophys. Res. Commun. 294(2):371–379; 2002.
41. Safford, K. M.; Safford, S. D.; Gimble, J. M.; Shetty, A. K.; Rice, H. E. Characterization of neuronal/glial differentiation of murine adipose-derived adult stromal cells. Exp. Neurol. 187(2):319–328; 2004.
42. Siminiak, T.; Kurpisz, M. Myocardial replacement therapy. Circulation 108(10):1167–1171; 2003.
43. Simmons, P. J.; Gronthos, S.; Zannettino, A.; Ohta, S.; Graves, S. Isolation, characterization and functional activity of human marrow stromal progenitors in hemopoiesis. Prog. Clin. Biol. Res. 389:271–280; 1994.
44. Simmons, P. J.; Masinovsky, B.; Longenecker, B. M.; Berenson, R.; Torok-Storb, B.; Gallatin, W. M. Vascular cell adhesion molecule-1 expressed by bone marrow stromal cells mediates the binding of hematopoietic progenitor cells. Blood 80(2):388–395; 1992.
45. Strem, B. M.; Hicok, K. C.; Zhu, M.; Wulur, I.; Alfonso, Z.; Schreiber, R. E.; Fraser, J. K.; Hedrick, M. H. Multipotential differentiation of adipose tissue-derived stem cells. Keio J. Med. 54(3):132–141; 2005.
46. Strem, B. M.; Zhu, M.; Alfonso, Z.; Daniels, E. J.; Schreiber, R.; Beygui, R.; MacLellan, W. R.; Hedrick, M. H.; Fraser, J. K. Expression of cardiomyocytic markers on adipose tissue-derived cells in a murine model of acute myocardial injury. Cytotherapy 7(3):282–291; 2005.
47. Strem, B. M.; Jordan, M. C.; Kim, J.; Yang, J.; Andersen, C. D.; Daniels, E.; Hedrick, M. H.; Roos, K. P.; Schreiber, R. E.; Fraser, J. K.; MacLellan, W. R. Adipose tissue-derived stem cells enhance cardiac function following surgically-induced myocardial infarction. Circulation 112(17 Suppl. II):274; 2005.
48. Sudhoff, T.; Sohngen, D. Circulating endothelial adhesion molecules (sE-selectin, sVCAM-1 and sICAM-1) during rHuG-CSF-stimulated stem cell mobilization. J. Hematother. Stem Cell Res. 11(1):147–151; 2002.
49. Tepliashin, A. S.; Korzhikova, S. V.; Sharifullina, S. Z.; Chupikova, N. I.; Rostovskaia, M. S.; Savchenkova, I. P. Characteristics of human mesenchymal stem cells isolated from bone marrow and adipose tissue. Tsitologiia 47(2): 130–135; 2005.
50. Valina, C. Intracoronary transplantation of autologous fat tissue derived mesenchymal stem cells in acute myocardial infarctions in pigs. Eur. Heart J. 25:48–49; 1995.
51. Watanabe, C. Intracoronary adipose tissue derivedstem cell therapy preserves left ventricular function in a porcine infarct model. Paper presented at Transvascular Cardiovascular Therapeutics Annual Meeting; 2004.
52. Wickham, M. Q.; Erickson, G. R.; Gimble, J. M.; Vail, T. P.; Guilak, F. Multipotent stromal cells derived from the infrapatellar fat pad of the knee. Clin. Orthop. Relat. Res. 412:196–212; 2003.
53. Xu, Y.; Malladi, P.; Wagner, D. R.; Longaker, M. T. Adipose-derived mesenchymal cells as a potential cell source for skeletal regeneration. Curr. Opin. Mol. Ther. 7(4): 300–305; 2005.
54. Yang, L.; Zheng, J.; Hui, G. Research progress of adipose tissue-derived stromal cells. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 18(4):331–334; 2004.
55. Yang, L.; Zheng, J.; Liu, X.; Hui, G.; Fei, J.; Guo, L. Adipose tissue-derived stromal cells differentiate into neuron-like cells. Sichuan Da Xue Xue Bao Yi Xue Ban 34(3):381–384; 2003.
56. Yoshimura, K.; Matsumoto, D.; Gonda, K. A clinical trial of soft-tissue augmentation by lipoinjection with adipose-derived stromal cells (ASCs). International Fat Applied Technology Society (IFATS); Third Annual Meeting: 9–10; 2005.
57. Zheng, B.; Cao, B.; Li, G.; Huard, J. Mouse adipose-derived stem cells undergo multilineage differentiation in vitro but primarily osteogenic and chondrogenic differentiation in vivo. Tissue Eng. 12(7):1891–1901; 2006.
58. Zuk, P. A.; Zhu, M.; Ashjian, P.; De Ugarte, D. A.; Huang, J. I.; Mizuno, H.; Alfonso, Z. C.; Fraser, J. K.; Benhaim, P.; Hedrick, M. H. Human adipose tissue is a source of multipotent stem cells. Mol. Biol. Cell 13(12): 4279–4295; 2002.
59. Zuk, P. A.; Zhu, M.; Mizuno, H.; Huang, J.; Futrell, J. W.; Katz, A. J.; Benhaim, P.; Lorenz, H. P.; Hedrick, M. H. Multilineage cells from human adipose tissue: Implications for cell-based therapies. Tissue Eng. 7(2):211–228; 2001.

CHAPTER 21

ADIPOSE DERIVED STEM CELLS: NEW KIDS ON THE BLOCK

Basic knowledge

EuroIntervention

Adipose derived stem cells: new kids on the block

E. Meliga[1,2], MD; H.J Duckers[1], MD, PhD; R.J. van Geuns[1], MD; E. Regar[1], MD, PhD; P. de Jaegere[1], MD, PhD; W. van der Giessen[1], MD, PhD; P.W. Serruys[1]*, MD, PhD

1. Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands; 2. Interventional Cardiology department, S. Giovanni Battista Hospital, University of Turin, Italy

All authors have no conflict of interest to declare.

KEYWORDS
Cell therapy, heart failure, adipose tissue, stem cells

Abstract

Heart failure is a major health problem and myocardial infarction (MI) is, at the present time, the main cause. Cell therapy hold great promise for use in tissue regeneration and is increasingly used in an effort to improve outcomes in cardiac disease. Recently it has been shown that adipose tissue, in addition to committed adipogenic, endothelial progenitor cells and pluripotent vascular progenitor cells, contains also multipotent cell types (adipose derived stem cells, ADSCs) that, in cell culture conditions, have extensive proliferative capacity and are able to differentiate into several lineages, mesenchymal or not.

ADSCs, similarly to MSCs, express the CD105, STRO1, CD166, CD117,CD90, CD54, CD44 and CD29 surface markers. Moreover, ADSCs are also capable of secreting a large number of growth factors, including vascular endothelial growth Factor, Granulocyte/Macrophage Colony Stimulating Factor, Stromal Derived Factor-1alpha and Hepatocyte Growing Factor.

Adipose tissue can be harvested in large amounts with minimal morbidity and, owing to the large concentration of stem cells contained in a typical harvest, therapeutic doses of ADSCs can easily be isolated in as little as an hour after liposuction, obviating the need for culture. Several studies conducted in porcine AMI models have shown a significant LV functional improvement, with no report of any potentially fatal arrhythmias. The APOLLO trial, a prospective, double blind, randomised, placebo controlled, sequential dose-escalation study conducted at the Thoraxcenter, Erasmus MC, will be the 'First-in-Man' study that will explore the safety and feasibility of ADSC transplantation in patients with acute MI.

* *Corresponding author: Thoraxcenter, Erasmus University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, The Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl*

Introduction

Despite recent developments in the treatment of coronary artery disease and the introduction of new devices and effective post PCI therapies, the loss of cardiac tissue and the resulting impairment of left ventricular function after myocardial infarction (MI) remains a main cause of heart failure, defining the need to find an effective treatment to ameliorate this major health problem and its economic consequences. The potential of cell transplantation to repair damaged myocardium is attractive and has been widely studied in both experimental and clinical conditions using various cell types[1-6]. The quest for the ideal cell is still ongoing, as the attributes of the ideal cell and working mechanism of cell regeneration still remain to be defined. Nonetheless, there appears to be a consensus that, among the cells effective in the treatment of heart disease, cells that are autologous, non-embryonic, do not require culturing to obtain a therapeutic dose, and can be administered during the same procedure, may be logistically easier to use and thus may have wider application in catheterisation laboratories.

The most extensively studied and characterised cells, that have been shown to have some of the above mentioned ideal properties, are mesenchymal stem cells (MSCs). MSCs are multipotent, adult stem cells, that can expand in cell culture and are able to differentiate into multiple cell phenotypes including bone, cartilage, neuronal and skeletal muscle progenitor cells, but also into vascular endothelial cells and cardiomyocytes[7-13].

Many previous cell therapy trials in patients with AMI, have been using mononucleated bone marrow derived cells (BMCs)[14-17], that consist of a heterogeneous cell population. A small fraction of these unfractioned BMCs are MSCs. Results of these trials showed an improvement of regional wall motion, global ejection fraction and, in some cases, a reduction of infarct size in the treated group[14,16]. Selected MSCs were evaluated by Chen and colleagues in 2004[18] in 34 patients demonstrating a significant improvement of regional wall motion, global ejection fraction, reduction of infarct size, but also reduction of left ventricular end diastolic volume (LVEDV) in the treated group, confirming the encouraging results obtained from previous preliminary animal studies[19-21]. So far, these cells have been harvested from bone marrow, however, limitations of this cell source are: 1) the number of MSCs in bone marrow is rather low; MSCs in fact represent <0.01% of all nucleated bone marrow cells in healthy volunteers (approximately 1 in 25,000 to 1 in 100,000)[22,23]; 2) donor site morbidity limits the amount of marrow that can be obtained (generally limited to no more than 40 ml)[24,25] and consequently 3) the long time required to obtain therapeutic cell doses by *ex vivo* cell expansion renders treatment in the acute phase of myocardial infarction impractical.

Recently it has been shown that adipose tissue, in addition to committed adipogenic, endothelial progenitor cells and pluripotent vascular progenitor cells, contains also multipotent cell types[26,27]. This finding has generated major interest because, in contrast to bone marrow, adipose tissue can be easily and safely harvested in large quantities and with minimal morbidity regardless of the condition of the patient, making it an appealing source for cell therapy.

Cell characteristics

Adipose tissue, differently from most tissues, has a remarkable plasticity during life. Although increases in volume can be partially obtained by increasing the amount of lipids stored in the already existing adipocytes (cellular hypertrophy), large increases in volume are usually associated with an increase in adipocyte count (cellular hyperplasia) accompanied by a concomitant expansion and remodelling of the microvasculature supplying these cells[28].

The hyperplastic process of the adipose tissue and supporting vascular bed is mediated by a cell population present within the stromal vascular fraction of adipose tissue generally referred to as adipose derived stem cells (ADSCs). These cells, previously supposed to be mono-potent adipocyte progenitor cells, called pre-adipocytes, have actually been demonstrated to have an impressive developmental plasticity[27,29] including the ability to undergo multi-lineage differentiation and self-renewal[26,30-32] (Figure 1).

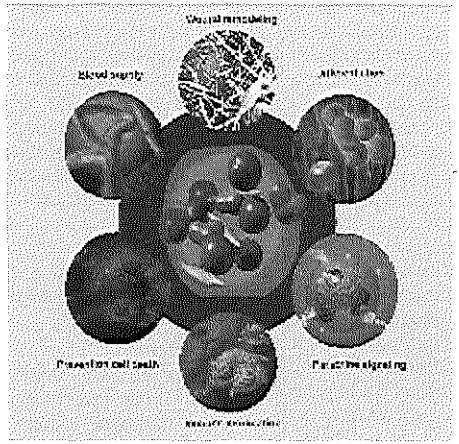


Figure 1. ADSCs actions end effects; ADSCs have an impressive developmental plasticity including the ability to undergo multi-lineage differentiation, to act by paracrine effects and to display an immuno-privileged behaviour.

ADSCs are a cell population with properties that are very similar, though not identical, to those of marrow derived MSCs[33-36]. These cells have extensive proliferative capacity and are able to differentiate in cell culture conditions into osteogenic, chondrogenic, myogenic lineages[7-13,37] and, more recently, into a neurogenic phenotype[9,38].

In culture, these cells express surface markers that are similar to those expressed by MSCs (Table 1): both cell types express CD105, STRO1 and CD166 (multi-lineage differentiation markers)[39-42], CD117 (stem cell factor receptor), CD90, CD54 (ICAM-1), CD44 and CD29 (beta-1 integrin)[13,43,44], whereas both cell types do not express the endothelial markers CD31, CD34 and the haematopoietic marker CD45[35,39] (Figure 2).

Recent studies showed that freshly isolated human ADSCs from subcutaneous adipose tissue tested positive for the aforementioned

Table 1. Cell surface characteristics of adipose derived stem cells and mesenchymal stem cells.

Cell-surface marker	ADSCs	MSCs
CD29	+	+
CD44	+	+
CD54	+	+
CD90	+	+
CD105	+	+
CD166	+	+
STRO-1	+	+
CD31	-	-
CD34	-	-
CD45	-	-
CD49D	+	-
CD106	-	+

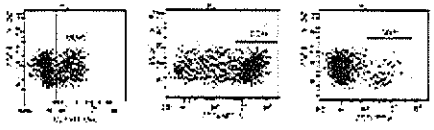


Figure 2. Representative sample of freshly isolated ADRCs. CD45+, CD34bright and CD31bright cells correspond to approximately 38.6, 56.5 and 6.8% of total cells. Cells were analysed using FACSDiva software (Picture from Cytori Therapeutics).

markers of haematopoietic and endothelial lineage. Flow cytometric characterisation of human ADSCs in culture revealed that the percentage of cells positive for CD34 expression decreased markedly after 1 week of culture[45] suggesting that the adhesion of ADSCs to plastic leads to a selection similar to that seen with MSCs, increasing the proportion of a unique population of cells with immature characteristics[46].

One of the most interesting differences in surface makers between MSCs and ADSCs is a reciprocal expression pattern of the very-late-activation antigen 4 or VLA-4 (CD49d/CD29) and its cognate receptor vascular cell- adhesion molecule 1 or VCAM-1 (CD106). ADSCs express VLA-4 but not VCAM-1 in the majority of donors, while MSCs usually express CD106, a component of VCAM-1, and not VLA-4[35].

The consequences of these properties are not clear yet and needs further investigation, but this observation is fascinating since both these molecules play an important role in haematopoietic stem cell homing and mobilisation from the bone marrow[47,48].

MSCs but also ADSCs are known to secrete a large number of angiogenesis-related cytokines[45]. In ADSCs in standard cultures, high levels of Hepatocyte Growth Factor (HGF), Vascular Endothelial Growth Factor (VEGF), Placental Growth Factor (PGF), Transforming Growth Factor-β (TGF-β), Fibroblast Growth Factor (FGF), Granulocyte/Macrophage Colony Stimulating Factor (GM-CSF), Monocyte Chemotactic Protein-1 (MCP-1) and Stromal Derived Factor-1alpha (SDF-1α) were observed, suggesting an active role of ADSCs in neovascularisation[45,49]. ADSCs and MSCs both possess the capability to suppress lymphocyte reaction in a dose-dependent and time dependent fashion; such immunosuppression probably occurs via the production of cytokines (including IL-4, IL-10, and TGF-β) responsible for the inhibition of lymphocyte proliferation[50,51].

Clonally-derived, multipotent cells from adipose tissue display furthermore an immuno-privileged behaviour[33]. Less than 1% of ADSCs in fact express the cell surface MHC class-I whereas class- II is almost absent[52]. Therefore ADSC are poorly recognised by T-lymphocytes, as suggested by the absence of infiltration by myeloid CD3 positive cells. When injected into immuno-competent X-linked muscular dystrophy (mdx) mouse muscles, ADSCs were seen to differentiate into functional muscle cells, integrated by fusing with host cells and were not rejected up to 6 months after transplantation[33]. This, together with the easy availability and the small amount of tissue needed for their isolation, suggests that, ADSCs might even have potential as immuno-privileged universal donor cells with the capacity to be used not only for autologous but also for allogeneic transplantation.

Harvest and expansion

Subcutaneous adipose tissue can be safely and quickly harvested in large quantities in several regions of the body, using conventional liposuction. A typical harvest out of 100-200 ml of human adipose tissue would yield about $50x10^6$ nucleated cells. During a regular liposuction procedure, it is not uncommon for plastic surgeons to remove in excess of 2,000 mL of fat. The samples are then enzymatically digested, filtered and centrifuged to separate the non-buoyant stromal cells from the buoyant adipocytes[46,53,54]. The non-buoyant fraction can yield in excess of $1x10^6$ stem cells (from 100 cc of fat tissue), about 45 fold more than a typical harvest of bone marrow aspiration (of 40 ml) which typically contains $2.5x10^4$ MSCs in a mature adult[25,55]. If necessary, the ADSC containing fraction can be cultured with different media (e.g. DMEM-F12; EGM-2-MV, α-MEM etc.) and supplemented with different percentages of serum and growth factors (e.g. VEGF, Insulin Like Growth Factor, bF Growth Factor etc.) to stimulate differentiation into dedicated lineages and expansion. (Figure 3) Owing to the great concen-

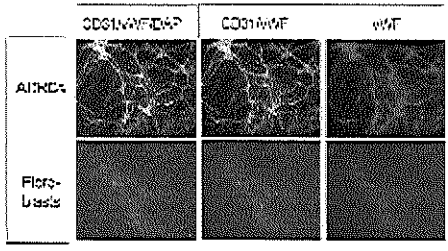


Figure 3. ADRCs form cords in an in vitro *tubule formation assay. ADRCs cultured for 1 week form cords in EGM-2. Immunofluorescence was used to detect CD31 (red) and von Willibrand factor (vWF, green). Cell nuclei were detected by DAPI (blue). Adult dermal fibroblasts were used as a control (bottom row).*

tration of ADSCs normally present in the adipose tissue harvest, it is also possible to instantaneously obtain therapeutic cell doses, with no need for further expansion in culture[56]. In contrast to BM-derived MSCs, therapeutic doses of ADSCs can easily be isolated in as little as an hour after liposuction[45,46]. This not only obviates the need for culture, but also avoids cell alterations associated with culturing.

Differentiation capabilities of ADSCs

Numerous studies have demonstrated that ADSCs, similarly to MSCs, have the capability to undergo differentiation into several cell types along both mesenchymal (fat, bone, cartilage muscle, nerve) and non-mesenchymal lineages (blood vessel)[7-13,36,57], demonstrating that adipose tissue actually contains pluripotent cells.

In particular, as far as muscle differentiation is concerned, evidence showed that ADSCs have the ability to differentiate into contractile cells with both striated muscle cells or cardiomyocytes features[53,58-62].

In vitro studies of ADSC differentiation

After two weeks of culture in RPMI medium, 20% to 30% of ADSCs increased in size, changed shape and began to beat spontaneously when observed under a phase contrast microscope by three weeks, as observed by Rangappa et al in 2003[57]. Likewise, after three weeks of exposure to rat cardiomyocytes conditioned DMEM medium, ADSCs expressed cardiomyocyte markers including sarcomeric alpha-actin, desmin, and cardiac troponin I, as well as the gap junction protein Connexin-43 (Cx-43) and started to beat spontaneously, as observed by Gaustad et al in 2004[58].

In 2005, Planat-Benard et al[53] obtained similar results by plating fresh ADSCs in a semi-solid culture. After three weeks of culture, ADSCs morphologically developed into ventricle-like, atrial-like and pacemaker-like cells, displaying tight inter-cellular connections (evidenced by Cx-43) and spontaneous, as well as triggered action potentials with beating. Moreover, these differentiated cells expressed the cardiac-specific transcription factors Nkx2.5, GATA-4, and MEF-2C, the structural cardiac proteins β-myosin heavy chain (MHC), myosin light chain-2 ventricular (MLC-2v), myosin light chain-2 atrial (MLC-2a) as well as the atrial natriuretic peptide (ANP), whereas the skeletal marker MyoD and smooth muscle actin were not expressed.

In vivo studies of ADSC differentiation

Several groups have so far reported data about the safety and efficacy of ADSCs to regenerate damaged myocardium in both small (rats) and large animals (pigs).

Delivery of ADSCs by intracoronary infusion to pigs two days after an acute MI through a LAD balloon occlusion (Watanabe et al, 2004) resulted in a 3% absolute increase in LVEF while the untreated pigs showed a 9% decline at 6-month FU ($P<0.01$)[59]. Likewise, intracoronary infusion of either ADSCs or MSCs in an acute MI pig model (Valina et al, 2004) resulted in a 11.4% improvement of absolute LVEF after 4 weeks, compared to only 2% improvement in the non-treated group ($P<0.003$)[60].

Strem and colleagues[61] in 2005 used intraventricular injections to deliver freshly isolated allogeneic ADSCs from Rosa 26 mice (expressing the beta-galactosidase transgene) into syngeneic recipient mice, following myocardial cryoinjury. Beta-galactosidase positive cells were found in treated mice together with the expression of MHC, Nkx2.5 and with troponin I at 14 days post transplantation, suggesting that ADSCs have the ability to engraft injured myocardium and express specific cardiomyocyte markers *in vivo*.

Freshly isolated ADSCs given immediately after reperfusion in a porcine AMI model (Alt et al) resulted in a 8% LVEF increase compared to controls at 8-week FU ($p=0.023$)[62].

Interestingly, concordant with the functional improvement, wall thickness and capillary density were both significantly increased in the border infarct areas of the treated group, compared to the control group[63].

In a study recently published by Miyahara and colleagues[54], ADSCs were transplanted directly onto infarcted murine hearts as a monolayered cell sheet. After transplantation, the engrafted sheet gradually grew to form a thick stratum that included newly formed vessels, undifferentiated cells and cardiomyocytes. Autologous transplantation of ADSC sheets, resulted in a decreased LVEDP, improved maximum and minimum dP/dt, increased diastolic wall thickness, increased left ventricular fractional shortening and decreased diastolic wall stress, as compared to dermal fibroblast sheets taken as a control.

Human studies of ADSC differentiation

ADSCs have been used successfully in a variety of indications in humans, including the treatment of Crohn's disease fistulas[64,65], osteogenesis imperfecta[66] and for breast augmentation and reconstruction after partial mastectomy[67]. So far, ADSCs have not been used to treat patients with MI or ischaemic heart disease. The APOLLO trial will be the 'First-in-Man' study that will explore the safety and feasibility of ADSC transplantation in patients with acute MI. This study is a prospective, double blind, randomised, placebo-controlled, sequential dose-escalation, study that will enrol up to 48 patients with acute MI at the Thoraxcenter, Erasmus MC, Rotterdam.

Eligible patients will be enrolled following primary PCI and will undergo liposuction and isolation of the adipose derived regenerative cells fraction (ADRCs) using the Celution™ system (Figure 4). ADRCs will then be injected within 24 hours from the primary PCI into the culprit coronary artery.

Main safety endpoints will include: major adverse cardiac or cerebral event (MACCE) rates, serious adverse events (SAEs)/adverse events (AEs) rates and a composite clinical endpoint of death, MI,

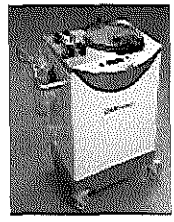


Figure 4. The Celution™ system, a fully automated device for the isolation of adipose derived and adipose regenerative stem cells.

stroke and re-hospitalisation for heart failure. Main feasibility endpoints are: absolute LVEF and changes in LVEF from baseline to six months; MI size; regional wall thickness and thickening in all segments; LV– end systolic volume (LV-ESV); LV– end diastolic volume (LV-EDV); and change in perfusion defect after revascularisation to six months as measured by contrast enhanced MRI, echocardiography and scintigraphy.

Patients will be followed for 36 months and will undergo imaging studies (2D/3D echocardiography, LV angiography, MRI, SPECT), functional evaluation (Left Ventricular Pressure-Volume Relationship), clinical evaluations and laboratory testing at six, 12 and 18 months.

Side effects, adverse events and potential hurdles

One of the biggest issues related to cell therapy is the potential arrhythmogenicity of the transplanted cells. Previous reports conducted using BMCs and skeletal myoblasts showed an increased incidence of arrhythmic events in the treated groups that often led to AICD implantation[68].

Though limited safety data are available to date, *in vivo* preliminary animal studies have not reported an increase in any potentially fatal arrhythmias.

Loop recorder monitoring in pigs treated with ADRCs[69] did not show an increase in arrhythmic events throughout the eight week follow-up period (one death in the control and ADRC group within the first week after MI). No sustained arrhythmias (e.g. bradycardia lower than 45/min or tachycardia above 165/min) were recorded in surviving animals. Moreover, at the end of the study period, programmed right ventricular stimulation failed to show an increase in susceptibility for arrhythmias by ADRC treatment. On the contrary, a significantly longer cycle length could be seen in the ADRC group at the beginning of an induced arrhythmia. This finding implies rather a reduction in the overall inducibility of malignant arrhythmias than an increase in susceptibility.

Issues associated with tissue harvest in patients with a recent AMI under high doses of anticoagulants, GP IIb-IIIa inhibitors and Aspirin are a potential concern, owing to the highly developed vascularisation of adipose tissue and the consequent bleeding risk. However, only a relatively small amount of tissue is required to obtain an effective cell dose, and haemostasis at the site of liposuction can easily be achieved by local pressure.

Conclusions

Human adipose tissue is a unique source of multi-potent stem cells that have the ability to differentiate into vascular and cardiomyocytes lineages, secrete several factors with angiogenic and anti-apoptotic effects and demonstrate stem cell-like extensive self-renewal. Moreover, ADSCs/ADRCs, unlike bone marrow-derived MSCs, can be easily and safely obtained in large numbers, without the necessity to culture.

ADRCs have been already used in humans in different clinical settings with excellent results and few side effects. Preclinical studies conducted in animal AMI models showed encouraging results and displayed their *in vivo* capability to differentiate into cardiac muscle cells as well as to excrete different growth factors with important pro-angiogenic effects that led to a significant improvement of ejection fraction and wall thickness.

The results of the APOLLO trial will provide an understanding of the real safety and efficacy of these cells in AMI patients, giving new insights on their possible future role in the treatment of cardiovascular disease.

References

1. Siminiak T, Kurpisz M. Myocardial replacement therapy. *Circulation.* 2003;108(10):1167-71.

2. Dimmeler S, Zeiher AM. Wanted! The best cell for cardiac regeneration. *J Am Coll Cardiol.* 2004;44(2):464-6.

3. Dimmeler S, Zeiher AM, Schneider MD. Unchain my heart: the scientific foundations of cardiac repair. *J Clin Invest.* 2005;115(3):572-83.

4. Laflamme MA, Murry CE. Regenerating the heart. *Nat Biotechnol.* 2005;23(7):845-56.

5. Edelberg JM, Xaymardan M, Rafii S, Hong MK. Adult cardiac stem cells—where do we go from here? *Sci Aging Knowledge Environ.* 2003;2003(26):PE17.

6. Rafii S, Lyden D. Therapeutic stem and progenitor cell transplantation for organ vascularization and regeneration. *Nat Med.* 2003;9(6):702-12.

7. Halvorsen YD, Franklin D, Bond AL, Hitt DC, Auchter C, Boskey AL, Paschalis EP, Wilkison WO, Gimble JM. Extracellular matrix mineralization and osteoblast gene expression by human adipose tissue-derived stromal cells. *Tissue Eng.* 2001;7(6):729-41.

8. Jiang Y, Jahagirdar BN, Reinhardt RL, Schwartz RE, Keene CD, Ortiz-Gonzalez XR, Reyes M, Lenvik T, Lund T, Blackstad M and others. Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature.* 2002;418(6893):41-9.

9. Safford KM, Hicok KC, Safford SD, Halvorsen YD, Wilkison WO, Gimble JM, Rice HE. Neurogenic differentiation of murine and human adipose-derived stromal cells. *Biochem Biophys Res Commun.* 2002;294(2):371-9.

10. Nagaya N, Kangawa K, Itoh T, Iwase T, Murakami S, Miyahara Y, Fujii T, Uematsu M, Ohgushi H, Yamagishi M and others. Transplantation of mesenchymal stem cells improves cardiac function in a rat model of dilated cardiomyopathy. *Circulation.* 2005;112(8):1128-35.

11. Yang L, Zheng J, Liu X, Hui G, Fei J, Guo L. [Adipose tissue-derived stromal cells differentiate into neuron-like cells]. *Sichuan Da Xue Xue Bao Yi Xue Ban.* 2003;34(3):381-4.

12. Xu Y, Malladi P, Wagner DR, Longaker MT. Adipose-derived mesenchymal cells as a potential cell source for skeletal regeneration. *Curr Opin Mol Ther.* 2005;7(4):300-5.

13. Fraser JK, Wulur I, Alfonso Z, Hedrick MH. Fat tissue: an underappreciated source of stem cells for biotechnology. *Trends Biotechnol.* 2006;24(4):150-4.

14. Assmus B, Schachinger V, Teupe C, Britten M, Lehmann R, Dobert N, Grunwald F, Aicher A, Urbich C, Martin H and others. Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI). *Circulation.* 2002;106(24):3009-17.

15. Wollert KC, Meyer GP, Lotz J, Ringes-Lichtenberg S, Lippolt P, Breidenbach C, Fichtner S, Korte T, Hornig B, Messinger D and others.

Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *Lancet.* 2004;364(9429):141-8.

16. Strauer BE, Brehm M, Zeus T, Kostering M, Hernandez A, Sorg RV, Kogler G, Wernet P. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. *Circulation.* 2002;106(15):1913-8.

17. Fernandez-Aviles F, San Roman JA, Garcia-Frade J, Fernandez ME, Penarrubia MJ, de la Fuente L, Gomez-Bueno M, Cantalapiedra A, Fernandez J, Gutierrez O and others. Experimental and clinical regenerative capability of human bone marrow cells after myocardial infarction. *Circ Res.* 2004;95(7):742-8.

18. Chen SL, Fang WW, Ye F, Liu YH, Qian J, Shan SJ, Zhang JJ, Chunhua RZ, Liao LM, Lin S, Sun JP. Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. *Am J Cardiol.* 2004;94:92-95.

19. Mangi AA, Noiseux N, Kong D, He H, Rezvani M, Ingwall JS, Dzau VJ. Mesenchymal stem cells modified with Akt prevent remodeling and restore performance of infarcted hearts. *Nat Med.* 2003;9(9):1195-201.

20. Makino S, Fukuda K, Miyoshi S, Konishi F, Kodama H, Pan J, Sano M, Takahashi T, Hori S, Abe H and others. Cardiomyocytes can be generated from marrow stromal cells *in vitro*. *J Clin Invest.* 1999;103(5):697-705.

21. Toma C, Pittenger MF, Cahill KS, Byrne BJ, Kessler PD. Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. *Circulation.* 2002;105(1):93-8.

22. Banfi A, Podesta M, Fazzuoli L, Sertoli MR, Venturini M, Santini G, Cancedda R, Quarto R. High-dose chemotherapy shows a dose-dependent toxicity to bone marrow osteoprogenitors: a mechanism for post-bone marrow transplantation osteopenia. *Cancer.* 2001;92(9):2419-28.

23. Banfi A, Bianchi G, Galotto M, Cancedda R, Quarto R. Bone marrow stromal damage after chemo/radiotherapy: occurrence, consequences and possibilities of treatment. *Leuk Lymphoma.* 2001;42(5):863-70.

24. Gluckman E, Horowitz MM, Champlin RE, Hows JM, Bacigalupo A, Biggs JC, Camitta BM, Gale RP, Gordon-Smith EC, Marmont AM and others. Bone marrow transplantation for severe aplastic anemia: influence of conditioning and graft-versus-host disease prophylaxis regimens on outcome. *Blood.* 1992;79(1):269-75.

25. Bacigalupo A, Tong J, Podesta M, Piaggio G, Figari O, Colombo P, Sogno G, Tedone E, Moro F, Van Lint MT and others. Bone marrow harvest for marrow transplantation: effect of multiple small (2 ml) or large (20 ml) aspirates. *Bone Marrow Transplant.* 1992;9(6):467-70.

26. Zuk PA, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, Benhaim P, Lorenz HP, Hedrick MH. Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng.* 2001;7(2):211-28.

27. Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, Alfonso ZC, Fraser JK, Benhaim P, Hedrick MH. Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell.* 2002;13(12):4279-95.

28. Ailhaud G, Grimaldi P, Negrel R. Cellular and molecular aspects of adipose tissue development. *Annu Rev Nutr.* 1992;12:207-33.

29. Katz AJ, Tholpady A, Tholpady SS, Shang H, Ogle RC. Cell surface and transcriptional characterization of human adipose-derived adherent stromal (hADAS) cells. *Stem Cells.* 2005;23(3):412-23.

30. Yang L, Zheng J, Hui G. [Research progress of adipose tissue-derived stromal cells]. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi.* 2004;18(4):331-4.

31. Zheng B, Cao B, Li G, Huard J. Mouse adipose-derived stem cells undergo multilineage differentiation *in vitro* but primarily osteogenic and chondrogenic differentiation *in vivo*. *Tissue Eng.* 2006;12(7):1891-901.

32. Teplyashin AS, Korzhikova SV, Sharifullina SZ, Chupikova NI, Rostovskaia MS, Savchenkova IP. [Characteristics of human mesenchymal stem cells isolated from bone marrow and adipose tissue]. *Tsitologiia.* 2005;47(2):130-5.

33. Rodriguez AM, Pisani D, Dechesne CA, Turc-Carel C, Kurzenne JY, Wdziekonski B, Villageois A, Bagnis C, Breittmayer JP, Groux H and others. Transplantation of a multipotent cell population from human adipose tissue induces dystrophin expression in the immunocompetent mdx mouse. *J Exp Med.* 2005;201(9):1397-405.

34. Rodriguez AM, Elabd C, Amri EZ, Ailhaud G, Dani C. The human adipose tissue is a source of multipotent stem cells. *Biochimie.* 2005;87(1):125-8.

35. De Ugarte DA, Alfonso Z, Zuk PA, Elbarbary A, Zhu M, Ashjian P, Benhaim P, Hedrick MH, Fraser JK. Differential expression of stem cell mobilization-associated molecules on multi-lineage cells from adipose tissue and bone marrow. *Immunol Lett.* 2003;89(2-3):267-70.

36. Wickham MQ, Erickson GR, Gimble JM, Vail TP, Guilak F. Multipotent stromal cells derived from the infrapatellar fat pad of the knee. *Clin Orthop Relat Res.* 2003(412):196-212.

37. Erickson GR, Gimble JM, Franklin DM, Rice HE, Awad H, Guilak F. Chondrogenic potential of adipose tissue-derived stromal cells *in vitro* and *in vivo*. *Biochem Biophys Res Commun.* 2002;290(2):763-9.

38. Safford KM, Safford SD, Gimble JM, Shetty AK, Rice HE. Characterization of neuronal/glial differentiation of murine adipose-derived adult stromal cells. *Exp Neurol.* 2004;187(2):319-28.

39. Gronthos S, Franklin DM, Leddy HA, Robey PG, Storms RW, Gimble JM. Surface protein characterization of human adipose tissue-derived stromal cells. *J Cell Physiol.* 2001;189(1):54-63.

40. Majumdar MK, Thiede MA, Mosca JD, Moorman M, Gerson SL. Phenotypic and functional comparison of cultures of marrow-derived mesenchymal stem cells (MSCs) and stromal cells. *J Cell Physiol.* 1998;176(1):57-66.

41. Dennis JE, Carbillet JP, Caplan AI, Charbord P. The STRO-1+ marrow cell population is multipotential. *Cells Tissues Organs.* 2002;170(2-3):73-82.

42. Simmons PJ, Gronthos S, Zannettino A, Ohta S, Graves S. Isolation, characterization and functional activity of human marrow stromal progenitors in hemopoiesis. *Prog Clin Biol Res.* 1994;389:271-80.

43. Strem BM, Hicok KC, Zhu M, Wulur I, Alfonso Z, Schreiber RE, Fraser JK, Hedrick MH. Multipotential differentiation of adipose tissue-derived stem cells. *Keio J Med.* 2005;54(3):132-41.

44. Fraser JK, Schreiber R, Strem B, Zhu M, Alfonso Z, Wulur I, Hedrick MH. Plasticity of human adipose stem cells toward endothelial cells and cardiomyocytes. *Nat Clin Pract Cardiovasc Med.* 2006;3 Suppl 1:S33-7.

45. Rehman J, Traktuev D, Li J, Merfeld-Clauss S, Temm-Grove CJ, Bovenkerk JE, Pell CL, Johnstone BH, Considine RV, March KL. Secretion of angiogenic and antiapoptotic factors by human adipose stromal cells. *Circulation.* 2004;109(10):1292-8.

46. Planat-Benard V, Silvestre JS, Cousin B, Andre M, Nibbelink M, Tamarat R, Clergue M, Manneville C, Saillan-Barreau C, Duriez M and oth-

ers. Plasticity of human adipose lineage cells toward endothelial cells: physiological and therapeutic perspectives. *Circulation.* 2004;109(5):656-63.

47. Sudhoff T, Sohngen D. Circulating endothelial adhesion molecules (sE-selectin, sVCAM-1 and sICAM-1) during rHuG-CSF-stimulated stem cell mobilization. *J Hematother Stem Cell Res.* 2002;11(1):147-51.

48. Simmons PJ, Masinovsky B, Longenecker BM, Berenson R, Torok-Storb B, Gallatin WM. Vascular cell adhesion molecule-1 expressed by bone marrow stromal cells mediates the binding of hematopoietic progenitor cells. *Blood.* 1992;80(2):388-95.

49. Rehman J, Considine RV, Bovenkerk JE, Li J, Slavens CA, Jones RM, March KL. Obesity is associated with increased levels of circulating hepatocyte growth factor. *J Am Coll Cardiol.* 2003;41(8):1408-13.

50. Von Herrath, M.G., and L.C. Harrison. 2003. Antigen-induced regulatory T cells in autoimmunity. *Nat. Rev. Immunol.* 3:223-232.

51. Puissant B, Barreau C, Bourin P, Clavel C, Corre J, Bousquet C, Taureau C, Cousin B, Abbal M, Laharrague P and others. Immunomodulatory effect of human adipose tissue-derived adult stem cells: comparison with bone marrow mesenchymal stem cells. *Br J Haematol.* 2005;129(1):118-29.

52. Lee RH, Kim B, Choi I, Kim H, Choi HS, Suh K, Bae YC, Jung JS. Characterization and expression analysis of mesenchymal stem cells from human bone marrow and adipose tissue. *Cell Physiol Biochem.* 2004;14(4-6):311-24.

53. Planat-Benard V, Menard C, Andre M, Puceat M, Perez A, Garcia-Verdugo JM, Penicaud L, Casteilla L. Spontaneous cardiomyocyte differentiation from adipose tissue stroma cells. *Circ Res.* 2004;94(2):223-9.

54. Miyahara Y, Nagaya N, Kataoka M, Yanagawa B, Tanaka K, Hao H, Ishino K, Ishida H, Shimizu T, Kangawa K and others. Monolayered mesenchymal stem cells repair scarred myocardium after myocardial infarction. *Nat Med.* 2006;12(4):459-65.

55. Muschler GF, Nitto H, Boehm CA, Easley KA. Age- and gender-related changes in the cellularity of human bone marrow and the prevalence of osteoblastic progenitors. *J Orthop Res.* 2001;19(1):117-25.

56. H. Duckers, K. Pinkernell, AM. Milstein, MH Hedrick. The Bedside Celution for Isolation of adipose derived regenerative cells. *EU.* 2006;2:395-398.

57. Rangappa S, Fen C, Lee EH, Bongso A, Sim EK. Transformation of adult mesenchymal stem cells isolated from the fatty tissue into cardiomyocytes. *Ann Thorac Surg.* 2003;75(3):775-9.

58. Gaustad KG, Boquest AC, Anderson BE, Gerdes AM, Collas P. Differentiation of human adipose tissue stem cells using extracts of rat cardiomyocytes. *Biochem Biophys Res Commun.* 2004;314(2):420-7.

59. Watanabe C (2004) Intracoronary adipose tissue derivedstem cell therapy preserves left ventricular function in a porcine infarct model. Paper presented at Transvascular Cardiovascular Therapeutics Annual Meeting, September 2004, Washington DC, USA.

60. Valina C (2004) Intracoronary transplantation of autologous fat tissue derived mesenchymal stem cells in acute myocardial infarctions in pigs [abstract]. *Eur Heart J.* 25 (Suppl):1995.

61. Strem BM, Zhu M, Alfonso Z, Daniels EJ, Schreiber R, Beygui R, MacLellan WR, Hedrick MH, Fraser JK. Expression of cardiomyocytic markers on adipose tissue-derived cells in a murine model of acute myocardial injury. *Cytotherapy.* 2005;7(3):282-91.

62. Alt E, Scharlau M, Pinkernell K, Amadi C, Reddy K, Matthias N, Daemen K, Fotuhi P. Uncultured, autologous adipose-derived stromal cells - a novel cell source for cardiac repair. *Am J Card.* 2005;96(7) (Suppl. I):71H.

63. Matthias N, Schwarzer M, Pinkernell K, Fotuhi P, Alt EU. Effect of Stem Cells on Left Ventricular Wall Thickness and Capillary Density in Pigs Following Myocardial Infarction. *JACC.* 2006;47(4):206A.

64. Garcia-Olmo D, Garcia-Arranz M, Herreros D, Pascual I, Peiro C, Rodriguez-Montes JA. A phase I clinical trial of the treatment of Crohn's fistula by adipose mesenchymal stem cell transplantation. *Dis Colon Rectum.* 2005;48(7):1416-23.

65. Garcia-Olmo D, Garcia-Arranz M, Garcia LG, Cuellar ES, Blanco IF, Prianes LA, Montes JA, Pinto FL, Marcos DH, Garcia-Sancho L. Autologous stem cell transplantation for treatment of rectovaginal fistula in perianal Crohn's disease: a new cell-based therapy. *Int J Colorectal Dis.* 2003;18(5):451-4.

66. Horwitz EM, Gordon PL, Koo WK, Marx JC, Neel MD, McNall RY, Muul L, Hofmann T: Isolated allogeneic bone marrow-derived mesenchymal cells engraft and stimulate growth in children with osteogenesis imperfecta: Implications for cell therapy of bone. *Proc Natl Acad Sci USA.* 2002;99:8932-8937.

67. Yoshimura K., Matsumoto D., Aiba E., Yamaoka H. and Nagase C. Lipoinjection with a Disposable Screw-Type Syringe for Soft-Tissue Augmentation 27 Yoshimura, K., Matsumoto, D., and Gonda K. A Clinical Trial of Soft-Tissue Augmentation by Lipoinjection with Adipose-Derived Stromal Cells (ASCs). International Fat Applied Technology Society (IFATS); Third Annual Meeting Sept 10 - 13, 2005, Charlottesville VA, p.9.

68. Makkar RR, Lill M, Chen PS. Stem cell therapy for myocardial repair: Is it arrhythmogenic? *J Am Coll Cardiol.* 2003;42(12):2070-2.

69. Fotuhi P, Scharlau M, Matthias N, Pinkernell K, Ferguson B, Alt E, Effects of Intracoronary Adipose Tissue Derived Stem Cell Transplantation on Sudden Cardiac Death and Fibrillation Cycle Length in Pigs with Myocardial Infarction. *Clinical Research in Cardiologie.* 2006;95(Suppl 5):P167.

CHAPTER 22

CLINICAL EXPERIENCE WITH AUTOLOGOUS MYOBLAST TRANSPLANTATION

EuroIntervention

Clinical experience with autologous myoblast transplantation

E. Meliga[1,3], MD; H.J Duckers[1], MD, PhD; R. Spencer[4]; P. Kalmucki[2], MD; P.W. Serruys[1], MD, PhD; T. Siminiak[2], MD, PhD

1. Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands; 2. Poznan University School of Medical Sciences, Cardiac and Rehabilitation Hospital Kowanowko, Poland; 3. Interventional Cardiology Department, S. Giovanni Battista Hospital, University of Turin, Italy; 4. Bioheart Inc., Sunrise, FL, USA

R. Spencer is an employee of Bioheart Inc. All other authors have no conflict of interest to declare.

KEYWORDS
Autologous myoblasts, cell therapy, transplantation, endo-ventricular approach

Abstract

Reperfusion and medical therapies are able to restore blood flow and to improve symptoms, functional class and in some cases increase survival. Cell therapy may be a potentially attractive approach to restore myocardial contractile performance after an infarction injury.

In the presence of fibrotic post-infarction scar with no detectable myocardial viability, direct myocyte precursors, i.e. myoblasts, are one of the first and still most encouraging cell types used in cell-based therapy, being considered as a potential source of new muscle fibres.

Direct intramyocardial myoblast injection during open-chest surgery or as a stand-alone percutaneous procedure has been shown to be feasible and safe in several animal and human clinical studies.

The present review explores the current clinical experience with autologous skeletal myoblasts transplantation in patients with post-infarction heart failure.

* *Corresponding author: Thoraxcenter, Erasmus University Medical Center, Rotterdam, PO Box 2040, 3000CA Rotterdam. The Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl*

Introduction

Heart failure is rapidly becoming a major worldwide epidemic and, in western countries, is by far the most common cause of hospitalisation. The increasing prevalence of heart failure directly relates to increasing age[1], a significant reduction in sudden cardiac death due to rapid revascularisation, the use of internal cardio-defibrillators (ICDs)[2] and improved long-term survival of patients with acute myocardial infarction (AMI).

Myocardial necrosis, and the subsequent formation of fibrotic scar which replaces viable myocardium, leads to depressed systolic function, reduced diastolic compliance, left ventricular remodelling, aneurysm formation and ultimately to the progression of congestive heart failure.

Revascularisation therapies have been able to restore perfusion and contractile function to post-infarct stunned or hibernated myocardium. Chronic medical therapies are further able to improve symptoms, functional class and, in some cases, increase survival, however these medical interventions are not capable of replacing or repairing damaged myocardial tissue. The potential to repair and grow new tissue within the necrotic scar as a result of cell transplantation has thus drawn widespread attention, resulting in several clinical studies sharing the common purpose of regenerating or repairing myocardium by the delivery of new contractile or pluripotent cells[3-10].

One of the first and still most encouraging cell types used in cell-based therapy are autologous skeletal muscle stem cells (also referred to as myoblasts). Skeletal myoblasts are mononuclear progenitor cells usually residing in a quiescent state between the basal membranes of skeletal muscle fibres. Following muscle injury, recruited non-contractile myoblasts proliferate and differentiate into functional (contractile) skeletal myocytes, ultimately fusing into multinucleated myotubes. When transplanted intra-miocardially, myoblasts have been shown to differentiate into myotubes[11-13] and contract synchronously with host cardiomyocytes, even in the absence of gap junctions.

The literature suggests that skeletal myotubes, in fact, are not capable of expressing the trans-membrane protein connexin 43 (Figure 1), a necessary element in achieving mechanical and electrical coupling with myocardial tissue, and thus do not couple with resident cardiomyocytes[14,15].

Nonetheless, myoblasts have been shown to actively contribute to systolic contraction. It was hypothesised that stretching signals and direct ionic trans-membrane currents[12,16] may enhance the contractile function within the area of fibrous post-infarction scar tissue with a lasting positive effect on global systolic function[17,18]. In addition to the aforementioned mechanical effects, myoblasts may improve cardiac function also by paracrine mechanisms. These cells are capable of secreting vascular endothelial growing factor (VEGF) and Insulin growth factor I (IGF-1) in concentrations which can mobilise resident quiescent cardiac cells and promote angiogenesis[19, 20]. Moreover, myoblast engraftment is associated with a marked attenuation of matrix metalloproteinase-2 and -9 up-regulation. This, together with VEGF and IGF-1 release, may protect peri-infarction tissues against fibrotic remodelling[21].

Cell therapies can be delivered via intracoronary injection, percutaneously by direct injection in the ventricular wall or with an open chest approach. While some cell types including bone marrow-derived and blood-derived endothelial progenitor cells[22] are capable of extravasating and migrating to ischaemic areas, skeletal myoblasts are not, making intracoronary delivery infeasible and even potentially harmful due to potential obstruction of the microcirculation and possible embolic micro-infarctions. In contrast, direct myoblast injection during open-heart surgery or as a stand alone percutaneous procedure has been shown to allow unrestricted cell uptake from the circulation without embolic risk in several animal and human clinical studies[8,23-25].

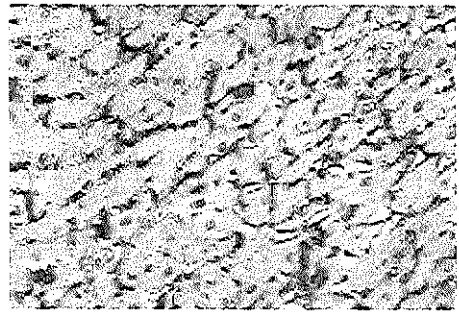


Figure 1. Formalin fixed paraffin embedded rat heart stained with Connexin 43 using LSAB-DAB. Note membrane staining pattern.

Cell transplantation during open heart surgery

The initial clinical experience with myoblast transplantation was achieved using trans-epicardial delivery during open-chest CABG surgery on patients with severely reduced LVEF[26-31]. This approach showed certain advantages, including easy access to the target area and delivery of a sufficient amount of cells per injection. Results from this early experience were encouraging. After the first case report on autologous skeletal myoblast transplantation was published in Lancet in 2001 by P. Menasché[28], two phase-I studies on the safety and efficacy of combined myoblast transplantation and CABG were started in Europe – Paris and Poznan – in 2002 and 2003, respectively[24-26]. Both studies showed the procedure to be safe and effective, providing a significant improvement in regional wall motion (by TTE) and global LVEF, as well as an increase in viability by positron emission tomography (PET) and a significant improvement in symptoms. These encouraging results were confirmed in the same year by Herreros and colleagues[27] in a population of twelve patients with previous MI and manifest ischaemic coronary artery disease. At 3 months, both regional and global LV function were increased (LV improved from 35.5±2.3% at baseline to 53.5±5% at 3 months), with viability of the treated cardiac tissue in the area of prior infarct area demonstrating improvement by PET. No cardiac arrhythmias were detected during the follow-up period. Long-term follow-up results from a multicentre, dose-escalating safety study of myoblast transplantation during CABG (24 patients) or LVAD implantation (6 patients) was also published in 2005 by Dib and colleagues[31]. Magnetic resonance imaging (MRI) scans, as well as echocardiographic and PET evaluations, showed increased via-

bility of the grafted scar and an improvement in the mean LVEF from 28% to 35% and 36%, after 1 and 2-year follow up, respectively. Further, histological analyses of hearts from patients undergoing LVAD treatment and subsequent heart transplantation, demonstrated survival and engraftment of skeletal myoblasts within the infarcted areas of the myocardium.

At the 2006 AHA meeting, Menaché and colleagues presented the six month follow-up of the MAGIC trial, a multi-centre, randomised, placebo-controlled trial designed to assess the safety and efficacy of two doses of myoblasts (high dose: $8x10^6$ cells and low dose: $4x10^6$ cells) injected concomitantly with CABG. The original study design called for 300 patients, however the trial was suspended following an interim analysis of the first 120 patients, as the study was not expected to meet its primary efficacy endpoint (regional and global wall motion improvement at six months by echo analysis). It is noteworthy, however, that evidence of positive remodelling presented in the $8x10^6$ cell group, as LVEDV, LVESV and LVEF improved significantly vs. control as measured by MUGA. Further, both the incidence of MACE and ventricular arrhythmias did not significantly differ between the treated and the control group, suggesting that the procedure is safe and not associated with an increased risk of arrhythmic events or sudden death. Though data deriving from the aforementioned trials are encouraging, many eligible patients who could potentially benefit from myoblast transplantation are not candidates for epicardial surgical delivery due to their clinical condition and the risks associated with surgery and general anaesthesia. Moreover, proper interpretation of the clinical outcomes obtained in these cell therapy studies is difficult because of the confounding and beneficial effect of the concomitant revascularisation procedure. Thus, a minimally invasive, catheter-based delivery approach is highly desirable. A percutaneous approach with cell injection as a stand alone procedure allows for targeting areas inaccessible by surgery (e.g. septum), treating high-risk patients and performing repeat injections with minimal risk. More importantly from a scientific perspective, percutaneous cell transplantation allows for the evaluation of intra myocardial myoblast implantation without confounding factors.

Endo-ventricular approach

Myoblasts delivery via endo-ventricular catheters allow direct cell injection into the targeted area of the injured left ventricular wall. Catheter-based trans-endocardial injection is performed using a needle catheter advanced across the aortic valve and positioned perpendicularly against the ventricular wall under fluoroscopic guidance or, in some cases, using an electromechanical mapping of the endocardial surface (NOGA) which is capable of defining viable and scarred myocardium (Figure 2)[8,32,33]. In 2003 the Rotterdam group[8] employed this technique to inject autologous myoblast suspensions into the area of post-infarction injury of five patients. This early experience, the first to document the feasibility of this particular approach, showed a significant increase in LV ejection fraction (LVEF) and regional wall motion at three months follow-up by angiography, as well as a trend towards increased LVEF as observed by angiography and nuclear scan at the six month follow-up.

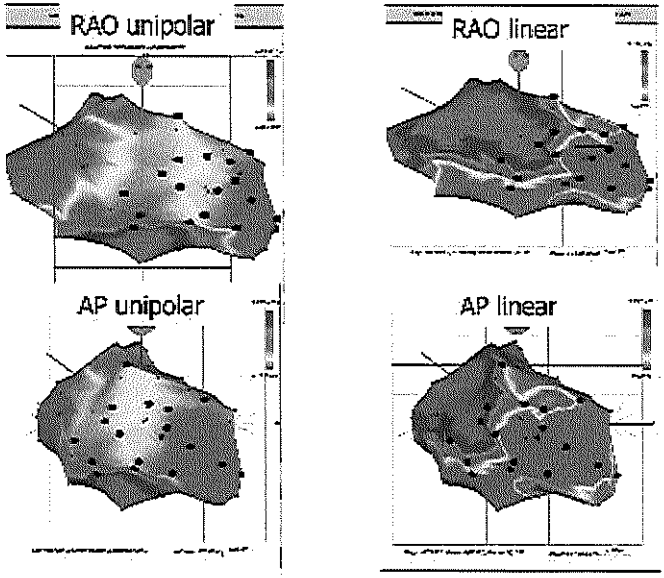


Figure 2. Unipolar (left) and linear (right) NOGA maps acquired during cell delivery procedure. The myocardial scar is scaled red indicating an area with a < 6 mV voltage and a < 2% shortening. Black dots indicate the trans-endocardial injection sites.

A sub-study conducted to evaluate the efficacy of myoblast transplantation on regional and global LV functional by dobutamine stress echocardiography with dobutamine infusion and tissue doppler imaging (TDI), likewise showed an improvement in the target wall systolic velocity and global LV function during low dose dobutamine infusion, indicating an improvement in the contractile reserve[34]. More impressively, these haemodynamic improvements were shown to persist one year after percutaneous myoblasts transplantation: pressure-volume loop analysis confirmed both systolic and the diastolic functional recovery (Figure 3)[35].

In 2004, Ince and colleagues published the results of a case control study in which myoblasts were injected in six post-AMI patients with severe chronic LV dysfunction. At 12 month follow up, LVEF of treated patients rose from 24±7% at baseline to 32±10% with a significant improvement of NYHA functional class, while in matched control patients LVEF decreased from 25±5% to 21±4% (p value <0,05) and NYHA functional class remained unchanged[23]. Similar results, though not as significantly pronounced, were observed by Serruys et al[36] in the first multicentre study (n=15) designed to assess the safety and feasibility of trans-endocardial myoblast injections. At 12 months follow-up, both regional wall motion scores and NYHA functional class were significantly improved while LVEF increased from 34±10% to 37±10% (p=0.26).

The safety and efficacy of skeletal myoblast transplantation using the Myocath® delivery system (Bioheart, Inc., Sunrise, FL, USA) is currently under investigation in two multicentre clinical trials ongoing in Europe (SEISMIC, phase II trial) and the US (MYOHEART, phase I trial). The SEISMIC trial will enrol 46 patients, randomised 2:1 to the Myocell™ treatment arm (n=30) versus optimised medical therapy controls (n=16). All patients will be analysed for six months. Recruitment for the MYOHEART study, a non-randomised trial, was recently completed. All patients will be analysed for 12 months, with the expected study completion date being November 2007. In each of the aforementioned studies, interim analysis data evaluated for DSMB review suggest positive trends towards improvement in treated patients especially respective to patient quality of life, though at this time these are statistically non-significant observations.

Although shown to be feasible and safe, cell delivery by percutaneous based injection requires further optimisation. It is challenging to consistently achieve full and stable apposition with the ventricular wall with most endo-ventricular catheter systems currently available as injection pressures can push back the needle tip from the myocardium, potentially allowing a back flush of cells from the puncture site to occur. In addition, following deployment, needle positioning against the endocardial surface does not synchronously follow the natural heart movement, which makes injection into thin post-infarction scars or in the border zone of the infarct difficult. In order to minimise these technical issues and to make the procedure easier, safer and more effective, a new generation of transendocardial delivery systems are being designed. The most prominent change consists of a different needle tip design: the traditional end hole needle has been replaced by a closed tip needle with side-port holes (e.g. Myocath™, Bioheart Inc.) In order to spread the cell injected over a larger target area, rather than relying solely on perpendicularity delivery to a single spot (Figure 4). This release pattern could diminish the risk of perforation and improve catheter stability with more reliable wall apposition by decreasing injection pressures and back flush.

Trans-venous approach

Catheter based cell infusion through coronary veins is a relatively novel approach.

The injection catheter, residing within a coronary vein and moving together with the heart wall, provides stability to the delivery system and allows an accurate and effective cell delivery, while minimising the possibility of cell loss and wall perforation.

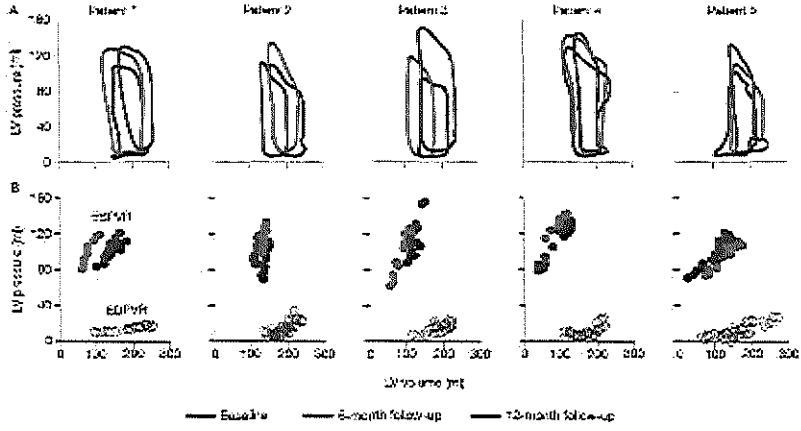


Figure 3. Steady-state pressure-volume loops (A), end-systolic pressure-volume relationship (ESPVR) and end-diastolic pressure-volume relationship (EDPVR) (B), for each patient. LV: left ventricular.

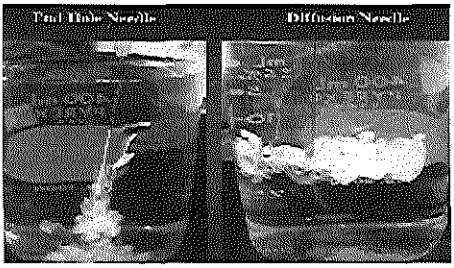


Figure 4. Old Myocath™ catheter with a single end hole needle (left) and the new Myocath™ delivery system with side port holes (right).

So far, the most compelling results using the trans-venous injection delivery in humans have been achieved by Slominak and co-workers[24,25] in the POZNAN trial[25], a phase one clinical trial designed to assess safety and feasibility of autologous myoblast transplantation performed by the TransAccess® catheter, a composite catheter system combining a phased array IVUS and a pre-shaped extendable 24 gauge nitinol needle.

The TransAccess system is placed in the target coronary vein (Figure 5), the intravascular orientation is performed using the corresponding artery, pericardium, and ventricular myocardium as landmarks with IVUS imaging (Figure 6). After verification of the proper TransAccess catheter position, the nitinol needle is extended into the myocardium and the injection catheter (MicroLume™) is advanced through the needle deep into the myocardial scar area, to allow myoblast suspension injection.

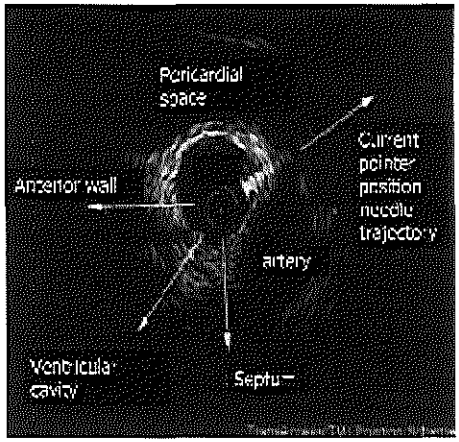


Figure 6. TransAccess® system orientation by IVUS imaging. The needle is oriented taking the corresponding artery, the pericardium, and the ventricular myocardium as landmarks.

The use of the anterior interventricular vein and the middle cardiac vein, parallel to the posterior descending coronary artery, both were shown to be feasible. Two to four intramyocardial injections were performed in each patient, delivering up to 100 million cells in 0.6 - 2.5 ml of saline solution. The procedure was reported to be technically successful in nine out of 10 patients and did not cause any periprocedural adverse event. At six months follow-up, NYHA class improved

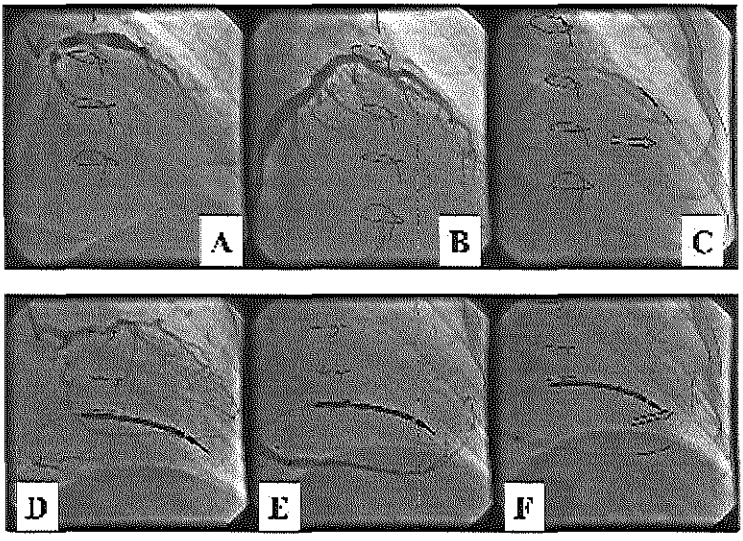


Figure 5. Trans-coronary-venous myoblast transplantation using anterior interventricular vein (A,B,C) and middle cardiac vein (D,E,F). A,C: coronary angiography; B,D: coronary venography, C,F: Trans Access® catheter system positioned within vein - arrow indicates tip of the microcatheter during cell injection.

in all patients and LVEF, assessed by echocardiography, significantly increased by three to eight percentage points in six out of nine patients, confirming both the safety and feasibility of trans-venous intramyocardial myoblast injections by the TransAccess® system.

Safety issues

While *ex vivo* experiments suggest the possibility of cell fusion and the formation of a synchronous beating network in a co-culture of myoblasts and cardiomyocytes[37,38], several studies have shown skeletal myotubes to be incapable of expressing connexin 43 (gap junction protein) and physically coupling with host cardiomyocytes, and from beating in synchrony with the rest of the heart[12,39,40].

In the absence of this electromechanical coupling, the arrhythmogenic mechanisms remain unclear. Myoblasts have been shown to generate burst of action potentials, which may induce ventricular extrasystoles and tachycardias through electro-tonic interactions[41]. Moreover, an arrhythmogenic role could be related to the injection procedure itself, including myocardial puncture, inflammatory response to injured transplanted myoblasts (paracrine effect) and immune reactions[41]. Major ventricular arrhythmias were observed in the majority of humans studies conducted thus far, irrespective of the delivery route or cell dose[8,25,26,28,31].

In the first clinical series published by Menasché at al[26], four patients who underwent autologous skeletal myoblast transplantations during CABG experienced sustained episodes of ventricular tachycardia (VT). Similarly, the possible arrhythmogenic effect has also been observed in studies using an endo-ventricular catheter approach. In the study conducted by Smits et al[42], one patient experienced sustained VT at six weeks and subsequently received subsequently an ICD, while more seriously, two sudden deaths occurred. These events prompted DSMB consultation and the recommendation for all subsequent patients to receive prophylactic ICD implantation. Interim results from the MAGIC trial presented at the AHA 2006 scientific session, however, suggested no statistically significant difference between the treatment and placebo groups in terms of ventricular arrhythmias. The interim analysis of the SEISMIC study suggests similar results. It should be emphasised that patients enrolled in these initial studies did not receive prophylactic antiarrhythmic therapy even though the target population of advanced ischaemic chronic heart failure easily develops ventricular arrhythmic events through the natural progression of the disease. Statistical analysis indicates that the risk of arrhythmic events is largely restricted to the first 30 days following the procedure, and recent clinical data suggest that prophylactic ICD implantation and use of Class III anti-arrhythmic medication may largely control risk of arrhythmias immediately following cell implantation.

Amiodarone was administered prophylactically to all patients in the POZNAN trial, and VT episodes occurred only in a single patient who was not compliant with amiodarone use during the first few weeks following the procedure[25]. In fact, it could be suggested that myoblast related VT may be circumvented by concomitant amiodarone therapy, thereby obviating an AICD implantation.

In sum, though several clinical trials in a small number of patients initially suggested a potential risk of ventricular arrhythmia following myoblast transplantation, it remains difficult to ascertain whether skeletal myoblasts are indeed arrhythmogenic as well as to unveil the underlying mechanism. Because the majority of episodes of ventricular arrhythmias occurred early after transplantation, it is plausible that their occurrence may be related to the procedure itself (due to the intramyocardial puncture or inflammatory reaction) rather than to the lack of gap junctions between the graft and host myocardium, which would result in later term arrhythmic events.

Conclusions

Although cell therapy for human cardiac regeneration is still an experimental field and only taking its first steps in clinical practice, a considerable number of preclinical animal studies and phase I human studies have been completed over the past years. These trials have shown that autologous myoblast transplantation, both during cardiac surgery and by percutaneous injection, is feasible, safe and appears to hold significant promise. However, the cell delivery still needs to be improved and the occurrence of arrhythmic complications needs to be observed carefully, with prophylactic attempts made to minimise their occurrence during the initial days following transplantation. Several large phase I/II clinical studies are currently under way in both Europe and the USA (e.g. SEISMIC and MYOHEART II) in order to assess the real potential arrhythmogenic effect as well as the efficacy of myoblast transplantation in chronic post-infarction myocardial injury. The final results from these trials will be available within the next year and will provide useful insight as to the possible future role of autologous myoblast therapy in the treatment of chronic heart failure.

References

1. Cohn JN, Francis GS. Cardiac failure: a revised paradigm. *J Card Fail.* 1995;1(4):261-6.

2. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* 2002;346(12):877-83.

3. Menasche P, Hagege AA, Scorsin M, Pouzet B, Desnos M, Duboc D, Schwartz K, Vilquin JT, Marolleau JP. Myoblast transplantation for heart failure. *Lancet.* 2001;357(9252):279-80.

4. Strauer BE, Brehm M, Zeus T, Kostering M, Hernandez A, Sorg RV, Kogler G, Wernet P. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. *Circulation.* 2002;106(15):1913-8.

5. Dimmeler S, Zeiher AM. Wanted! The best cell for cardiac regeneration. *J Am Coll Cardiol.* 2004;44(2):464-6.

6. Rafii S, Lyden D. Therapeutic stem and progenitor cell transplantation for organ vascularization and regeneration. *Nat Med.* 2003;9(6):702-12.

7. Perin EC, Dohmann HF, Borojevic R, Silva SA, Sousa AL, Mesquita CT, Rossi MI, Carvalho AC, Dutra HS, Dohmann HJ and others. Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure. *Circulation.* 2003;107(18):2294-302.

8. Smits PC, van Geuns RJ, Poldermans D, Bountioukos M, Onderwater EE, Lee CH, Maat AP, Serruys PW. Catheter-based intramyocardial injection of autologous skeletal myoblasts as a primary treatment of ischemic heart failure: clinical experience with six-month follow-up. *J Am Coll Cardiol.* 2003;42(12):2063-9.

9. Assmus B, Schachinger V, Teupe C, Britten M, Lehmann R, Dobert N, Grunwald F, Aicher A, Urbich C, Martin H and others. Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI). *Circulation.* 2002;106(24):3009-17.

10. Wollert KC, Meyer GP, Lotz J, Ringes-Lichtenberg S, Lippolt P, Breidenbach C, Fichtner S, Korte T, Hornig B, Messinger D and others. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *Lancet.* 2004;364(9429):141-8.

11. Ghostine S, Carrion C, Souza LC, Richard P, Bruneval P, Vilquin JT, Pouzet B, Schwartz K, Menasche P, Hagege AA. Long-term efficacy of myoblast transplantation on regional structure and function after myocardial infarction. *Circulation.* 2002;106(12 Suppl 1):I131-6.

12. Leobon B, Garcin I, Menasche P, Vilquin JT, Audinat E, Charpak S. Myoblasts transplanted into rat infarcted myocardium are functionally isolated from their host. *Proc Natl Acad Sci USA.* 2003;100(13):7808-11.

13. Pagani FD, DerSimonian H, Zawadzka A, Wetzel K, Edge AS, Jacoby DB, Dinsmore JH, Wright S, Aretz TH, Eisen HJ and others. Autologous skeletal myoblasts transplanted to ischemia-damaged myocardium in humans. Histological analysis of cell survival and differentiation. *J Am Coll Cardiol.* 2003;41(5):879-88.

14. Reinecke H, Minami E, Virag JI, Murry CE. Gene transfer of connexin43 into skeletal muscle. *Hum Gene Ther.* 2004;15(7):627-36.

15. Reinecke H, Murry CE. Transmural replacement of myocardium after skeletal myoblast grafting into the heart. Too much of a good thing? *Cardiovasc Pathol.* 2000;9(6):337-44.

16. Hagege AA, Vilquin JT, Bruneval P, Menasche P. Regeneration of the myocardium: a new role in the treatment of ischemic heart disease? *Hypertension.* 2001;38(6):1413-5.

17. Ravens U. [Electrophysiological properties of stem cells]. *Herz.* 2006;31(2):123-6.

18. Scorsin M, Hagege A, Vilquin JT, Fiszman M, Marotte F, Samuel JL, Rappaport L, Schwartz K, Menasche P. Comparison of the effects of fetal cardiomyocyte and skeletal myoblast transplantation on postinfarction left ventricular function. *J Thorac Cardiovasc Surg.* 2000;119(6):1169-75.

19. Xia JH, Xie AN, Zhang KL, Xu L, Zheng XY. The vascular endothelial growth factor expression and vascular regeneration in infarcted myocardium by skeletal muscle satellite cells. *Chin Med J (Engl).* 2006;119(2):117-21.

20. Hill E, Boontheekul T, Mooney DJ. Regulating activation of transplanted cells controls tissue regeneration. *Proc Natl Acad Sci USA.* 2006;103(8):2494-9.

21. Murtuza B, Suzuki K, Bou-Gharios G, Beauchamp JR, Smolenski RT, Partridge TA, Yacoub MH. Transplantation of skeletal myoblasts secreting an IL-1 inhibitor modulates adverse remodeling in infarcted murine myocardium. *Proc Natl Acad Sci USA.* 2004;101(12):4216-21.

22. Aicher A, Brenner W, Zuhayra M, Badorff C, Massoudi S, Assmus B, Eckey T, Henze E, Zeiher AM, Dimmeler S. Assessment of the tissue distribution of transplanted human endothelial progenitor cells by radioactive labeling. *Circulation.* 2003;107(16):2134-9.

23. Ince H, Petzsch M, Rehders TC, Chatterjee T, Nienaber CA. Transcatheter transplantation of autologous skeletal myoblasts in postinfarction patients with severe left ventricular dysfunction. *J Endovasc Ther.* 2004;11(6):695-704.

24. Siminiak T, Fiszer D, Jerzykowska O, Grygielska B, Kalmucki P, Kurpisz M. Percutaneous autologous myoblast transplantation in the treatment of post-infarction myocardial contractility impairment—report on two cases. *Kardiol Pol.* 2003;59(12):492-501.

25. Siminiak T, Fiszer D, Jerzykowska O, Grygielska B, Rozwadowska N, Kalmucki P, Kurpisz M. Percutaneous trans-coronary-venous transplantation of autologous skeletal myoblasts in the treatment of post-infarction myocardial contractility impairment: the POZNAN trial. *Eur Heart J.* 2005;26(12):1188-95.

26. Menasche P, Hagege AA, Vilquin JT, Desnos M, Abergel E, Pouzet B, Bel A, Sarateanu S, Scorsin M, Schwartz K and others. Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction. *J Am Coll Cardiol.* 2003;41(7):1078-83.

27. Herreros J, Prosper F, Perez A, Gavira JJ, Garcia-Velloso MJ, Barba J, Sanchez PL, Canizo C, Rabago G, Marti-Climent JM and others. Autologous intramyocardial injection of cultured skeletal muscle-derived stem cells in patients with non-acute myocardial infarction. *Eur Heart J.* 2003;24(22):2012-20.

28. Menasche P, Hagege A, Scorsin M, Pouzet B, Desnos M, Duboc D, Schwartz K, Vilquin JT, Marolleau JP. [Autologous skeletal myoblast transplantation for cardiac insufficiency. First clinical case]. *Arch Mal Coeur Vaiss.* 2001;94(3):180-2.

29. Chachques JC, Herreros J, Trainini J, Juffe A, Rendal E, Prosper F, Genovese J. Autologous human serum for cell culture avoids the implantation of cardioverter-defibrillators in cellular cardiomyoplasty. *Int J Cardiol.* 2004;95 Suppl 1:S29-33.

30. Dib N, McCarthy P, Campbell A, Yeager M, Pagani FD, Wright S, MacLellan WR, Fonarow G, Eisen HJ, Michler RE and others. Feasibility and safety of autologous myoblast transplantation in patients with ischemic cardiomyopathy. *Cell Transplant.* 2005;14(1):11-9.

31. Dib N, Michler RE, Pagani FD, Wright S, Kerelakes DJ, Lengerich R, Binkley P, Buchele D, Anand I, Swingen C and others. Safety and feasibility of autologous myoblast transplantation in patients with ischemic cardiomyopathy: four-year follow-up. *Circulation.* 2005;112(12):1748-55.

32. Sarmento-Leite R, Silva GV, Dohman HF, Rocha RM, Dohman HJ, de Mattos ND, Carvalho LA, Gottschall CA, Perin EC. Comparison of left ventricular electromechanical mapping and left ventricular angiography: defining practical standards for analysis of NOGA maps. *Tex Heart Inst J.* 2003;30(1):19-26.

33. Fuchs S, Satler LF, Kornowski R, Okubagzi P, Weisz G, Baffour R, Waksman R, Weissman NJ, Cerqueira M, Leon MB and others. Catheter-based autologous bone marrow myocardial injection in no-option patients with advanced coronary artery disease: a feasibility study. *J Am Coll Cardiol.* 2003;41(10):1721-4.

34. Biagini E, Valgimigli M, Smits PC, Poldermans D, Schinkel AF, Rizzello V, Onderwater EE, Bountioukos M, Serruys PW. Stress and tissue Doppler echocardiographic evidence of effectiveness of myoblast transplantation in patients with ischaemic heart failure. *Eur J Heart Fail.* 2006.

35. Steendijk P, Smits PC, Valgimigli M, van der Giessen WJ, Onderwater EE, Serruys PW. Intramyocardial injection of skeletal myoblasts: long-term follow-up with pressure-volume loops. *Nat Clin Pract Cardiovasc Med.* 2006;3 Suppl 1:S94-100.

36. Smits P, Nienaber C, Colombo A, Ince H, Carlino M, Theuns D, Biagini E, Valgimigli M, Onderwater E, Steendijk P, Peters N, Goedhart D, Serruys PW. Myocrdial repair by percutaneous cell transplantation of autologous skeletal myoblast as a stand alone procedure in post myocardial infarction chronic heart failure patients. *EU.* 2006:1:417-424

37. Reinecke H, Minami E, Poppa V, Murry CE. Evidence for fusion between cardiac and skeletal muscle cells. *Circ Res.* 2004;94(6):e56-60.

38. Reinecke H, MacDonald GH, Hauschka SD, Murry CE. Electromechanical coupling between skeletal and cardiac muscle. Implications for infarct repair. *J Cell Biol.* 2000;149(3):731-40.

39. Rubart M, Soonpaa MH, Nakajima H, Field LJ. Spontaneous and evoked intracellular calcium transients in donor-derived myocytes following intracardiac myoblast transplantation. *J Clin Invest.* 2004;114(6):775-83.

40. Tolmachov O, Ma YL, Themis M, Patel P, Spohr H, Macleod KT, Ullrich ND, Kienast Y, Coutelle C, Peters NS. Overexpression of connexin 43 using a retroviral vector improves electrical coupling of skeletal myoblasts with cardiac myocytes *in vitro*. *BMC Cardiovasc Disord.* 2006;6:25.

41. Makkar RR, Lill M, Chen PS. Stem cell therapy for myocardial repair: is it arrhythmogenic? *J Am Coll Cardiol.* 2003;42(12):2070-2.

42. Smits P, Nienaber C, Colombo A, Ince H, Carlino M, Theuns D, Biagini E, Valgimigli M, Onderwater E, Steendijk P, Peters N, Goedhart D, Serruys PW. Myocrdial repair by percutaneous cell transplantation of autologous skeletal myoblast as a stand alone procedure in post myocardial infarction chronic heart failure patients. *EIJ.* 2006:1:417-424

CHAPTER 23

PERCUTANEOUS TRANSPLANTATION OF SKELETAL MYOBLAST IN THE TREATMENT OF POST-INFARCTION INJURY

EUROPEAN SOCIETY OF CARDIOLOGY®

Percutaneous transplantation of skeletal myoblast in the treatment of post-infarction injury

Tomasz Siminiak[1]*, Emanuele Meliga[2], Olga Jerzykowska[1], and Patrick W. Serruys[2]

[1] *Department of Cardiology, Poznań University of Medical Sciences, Cardiac and Rehabilitation Hospital, ul. Sanatoryjna 34, 64-600 Kowanówko k/Obornik Wlkp, Poland*
[2] *Department of Cardiology, Thorax Center, Erasmus Medical Center, Rotterdam, The Netherlands*

KEYWORDS
Heart failure;
Myoblasts;
Cell transplantation;
Catheter systems

Cell therapy may be a potentially attractive approach to restore myocardial contractile performance after an infarction injury. Multipotent stem cells are currently being studied as a possible cell source for myocardial repair within the first few days after the infarction onset in non-revascularizable areas of the left ventricle having viable myocardium. In the presence of fibrotic post-infarction scar with no detectable myocardial viability, direct myocyte precursors, i.e. myoblasts, are being considered as a potential source of new muscle fibres. We review the current clinical experience with transplantation of the autologous skeletal myoblasts in patients with post-infarction heart failure, focusing on percutaneous cell transplantations performed as a sole procedure.

Introduction

Despite the recent developments in the treatment of coronary artery disease, congestive heart failure caused by myocardial infarction still remains a major health problem, affecting millions of patients worldwide with massive negative economic consequences. Myocardial necrosis and subsequent formation of fibrotic scar that replaces viable myocardium may lead to depressed systolic function, left ventricular (LV) remodelling, aneurysm formation, and ultimately to congestive heart failure. In the last few decades, improved treatments and an ageing population has lead to longer post-myocardial infarction survival resulting in increased prevalence of post-ischaemic heart failure.[1] Consequently, the treatment of heart failure has gained widespread attention.

The possibility of repairing and growing new myocardium within the necrotic tissue as a result of cell transplantation has been widely studied in both experimental and clinical conditions.[2–7]

Among the variety of cells studied, autologous skeletal myoblasts are one of the most encouraging cell sources for cardiac repair. Skeletal myoblasts, or satellite cells, are progenitor cells usually residing in a quiescent state under the basal membrane of skeletal muscle fibres, until recruited to proliferate and differentiate into mature skeletal myocytes in response to injuries (*Figure 1*). They are of their autologous origin, the ability to be amplified *in vitro*, and have high proliferative potential resistance to ischaemia and preclinical efficacy.[8] These characteristics have led clinical investigators to evaluate the effect of transplanted autologous myoblasts in patients with post-infarction heart failure. Myoblasts differentiate into myotubes and maintain muscle properties when transplanted into an infarct area.[9–11]

Electromechanical properties of myocardial and skeletal muscle tissues differ significantly. Cardiac cells act together synchronously due to the presence of special cell-to-cell junctions containing N-cadherin and connexin 43[12,13] (*Figure 2*). The latter is a transmembrane protein playing an important role in mechanical and electrical coupling within cardiac tissue.[14] The lack of gap junction protein expression like connexin 43 on skeletal myotubes prevents them from being physically coupled with host cardiomyocytes, suggesting that these cells do not beat in synchrony with the rest of the heart.[10,15,16]

* Corresponding author. Tel: +48 602217202; fax: +48 612977500.
E-mail address: tomasz.siminiak@usoms.poznan.pl

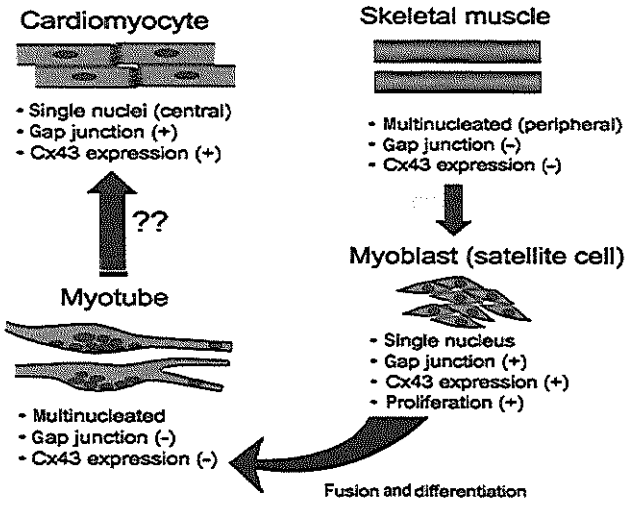


Figure 1 Myoblasts are usually in a quiescent state under the basal membrane of skeletal muscle fibres. After being gathered and expanded, myoblasts are transplantated into an infarct area where they differentiate into myotubes and maintain muscle properties. It is still unclear whether myoblasts can transdifferentiate into cardiomyocytes.

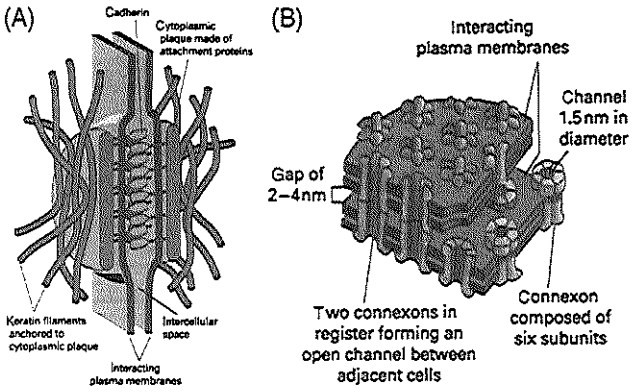


Figure 2 Cell to cell junction. Cadherin (A) has an important structural role linking the cytoplasmatic plaque on the inner side and coupling with other catherins on the extracellular side. Connexon 43 (B) is composed of six subunits and forms channels between cardiac cells in order to create an electrical coupling.

However, it has been shown that the lack of junctions between grafted cells and host tissue does not preclude improvement in LV contractile function.[17] It has been suggested that transplanted cells can contract synchronously even in the absence of connections between cells, probably by stretching or by direct transmembrane channelling of electric currents.[10,18] The direct contribution of these engrafted cells in improving systolic function was noticed in several studies that indicated a positive effect of skeletal myoblasts on myocardial contractility lasting over time and correlating with the number of implanted cells.[19,20] Although certain *ex vivo* data suggest that skeletal myoblasts may acquire few characteristics of cardiomyocytes or may fuse with them forming *chimeric cells*,[21] it has been assumed that the grafted cells do not transdifferentiate, instead retaining the morphological and electrophysiological properties of skeletal muscle.[9,17]

The capability of myoblasts to improve cardiac function cannot be explained only in terms of electromechanical integration or direct contribution. Other mechanisms were found to play an important role. One

hypothesis proposes that the engrafted cells could affect post-infarction remodelling by limiting the expansion of the post-infarction scar.[22–24] A second possible mechanism is the paracrine effect that myoblasts exert on surrounding myocardial cells. This hypothesis is derived from the observation that these cells are able to release pleiotrophic factors such as vascular endothelial growth factor and insulin growth factor I that could mobilize resident quiescent cardiac cells and promote angiogenesis.[25–27] These factors in association with a marked attenuation of matrix metalloproteinase-2 and -9 up-regulation may work as antifibrotic agents protecting peri-infarction tissues.[28]

Since skeletal myoblasts do not extravasate and may cause microembolizations after intracoronary delivery, their potential application in myocardial regeneration requires direct cell injection into the area of damaged myocardium. Transepicardial cell injection during open-chest surgery and several catheter-based methods have been proposed and studied in clinical trials.[8,29–33] (*Figures 3* and *4*).

Initial clinical experience: open-chest myoblast transplantation

The first report on autologous skeletal myoblast transplantation during open-chest cardiac surgery was published in the *Lancet* in 2001 by Menasché *et al.*[34] After that case report, two small phase-one clinical trials were started in Paris and Poznan.[8,35] In both trials, 10 patients with severely reduced LVEF undergoing CABG received transepicardial myoblast injection. Five months after the procedure, a significant improvement in symptoms by one NYHA class, an increase of regional wall motion, an increase of global LV ejection fraction (LVEF) as well as an increase in tracer activity on positron emission tomography (PET) were observed, suggesting a new onset of metabolic activity in the previously non-viable scar area. However, 4 years after combined myoblast transplantation and CABG, in almost one-third of the Poznan series the end-diastolic LV diameter was increased (unpublished own observation) generating doubts about the previously reported capability of transplanted cells to reduce ventricular dilation.[23,24] In two other similar phase-one studies published by Herreros *et al.*[30] and Chachques *et al.*,[32] a total of 21 patients received myoblast injection during CABG. Consistent with prior studies, improvements of regional wall motion and global LVEF were noted, suggesting safety and feasibility of the method.

In a recent multicentre dose-escalating safety trial conducted in the USA, published by Dib *et al.*,[36,37] 11 patients underwent myoblast transplantation during open-chest surgery. The echocardiographic evaluation as well as PET and magnetic resonance imaging (MRI) scans showed an increased viability of grafted scar, whereas the mean EF improved from 22.7 to 35.9%.

In 2004, Menasché *et al.* started the MAGIC trial, a multicentre, prospective, randomized, double-blind, placebo-controlled trial designed to evaluate the effects of skeletal myoblast transplantation in the context of severe ischaemic heart failure in a population of 300 selected patients. The study was prematurely discontinued in February 2006 after 120 patients were enrolled (97 treated) because of the high incidence of ventricular arrhythmias. The assessment of the risk/benefit ratio is currently under way and the trial could be resumed after the approval of the Data Monitoring Committee.

Cell transplantation during cardiac surgery has certain advantages including easy access to the target area and possible delivery of large numbers of cells per unit. However, direct transepicardial approach may cause additional risk to the patient during surgery, since candidates for cell transplantation often have a history of multiple infarctions and LV dysfunction, and clinical symptoms of severe heart failure. Moreover, the interpretation of clinical outcomes obtained from trials evaluating myoblast injection during CABG is not possible because the effects of the two procedures performed at the same time cannot be easily distinguished and ascertained. However, in light of these limitations and of the trend towards less-invasive, diagnostic, and therapeutic procedures, percutaneous approaches with cell injection as a sole procedure are under investigation.

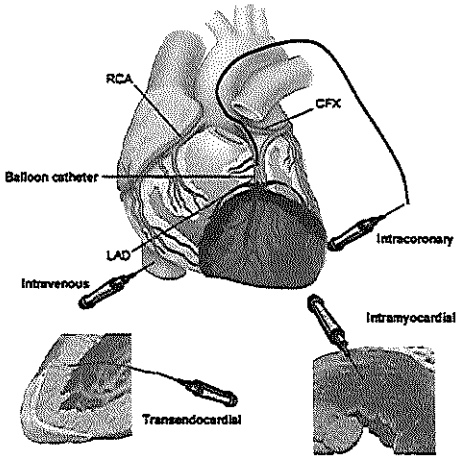


Figure 3 Myoblast-delivering approaches.

Percutaneous myoblast transplantation: cell injection as a sole procedure

Catheter-based transendocardial or transcoronary vein injections, performed as a sole therapy, may allow the evaluation of effect of myoblasts without confounders. It may also enable repeated cell injections in patients with severe myocardial injuries, since excessive number of transplanted cells in a single injection may result in only a small percentage of grafted cells survived. In fact, despite more than 10 years of work in this field,

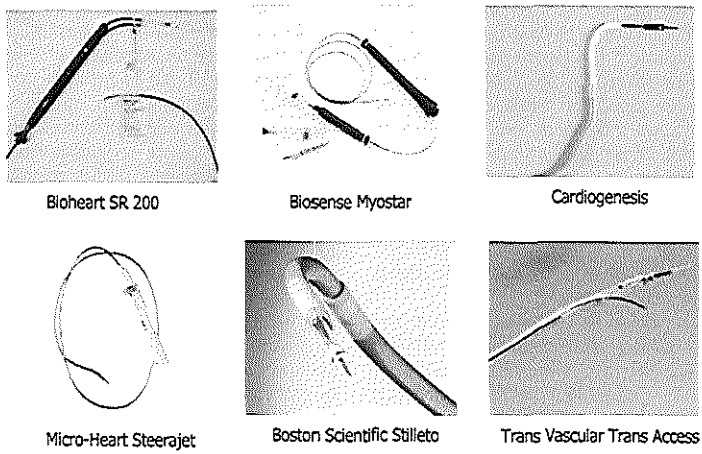


Figure 4 Different *trans*-endocardial and *trans*-coronary-venous cell delivery systems used in recent trials.

the delivering technique has still to be improved; about 90% of successfully delivered cells leak back out of the injection site or die within the first week.[38] Direct cell injection in the ventricular wall can be achieved both by a transendocardial[29] or a transcoronary vein approach.[33,39]

Catheter-based transendocardial injection is performed using a needle catheter directed perpendicularly to the inner surface of the target area using an electromechanical mapping of the endocardial surface.[40–42] Although this technique has been demonstrated to be feasible, cell delivery by direct injection may be difficult: endoventricular catheter systems currently available have limited stability so that a back-flush of cells from the puncture site is to be expected. In addition, the needle positioned against the endocardial surface does not follow the heart movements making the injection in thinned post-infarction scars or in the border zone of the infarct very challenging.

Catheter-based cell infusion through coronary veins is a relatively new approach recently used in a pilot trial by Siminiak *et al.*[43] and it consists of a catheter-based endovascular system incorporating an IVUS source and an extendable needle (TransAccess, Trans Vascular, Menlo Park, CA, USA). The TransAccess catheter is a monorail, composite catheter system combining both a phased array IVUS and a pre-shaped adjustable nitinol needle. After placing the TransAccess system in the target coronary vein through the coronary sinus, the needle is oriented using IVUS images of the corresponding artery, the pericardium, and the ventricular myocardium as landmarks (*Figure 5*). The nitinol needle is extended into the myocardium and a micro-infusion catheter (IntraLume, TransVascular Inc.) is then advanced through the needle while simultaneously injecting of the therapeutic agent. In contrast to the transendocardial approach, where cells are injected perpendicularly, the TransAccess system delivers cells parallel to the ventricular wall.

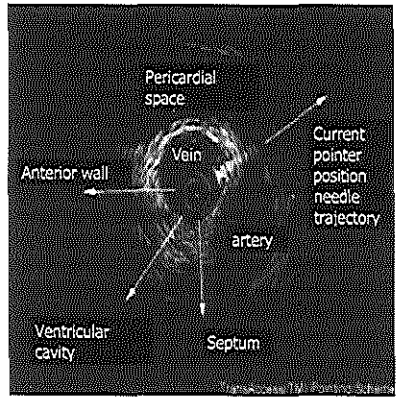


Figure 5 IVUS image of the TransAccess system in a coronary vein. The needle is oriented using IVUS imaging taking the corresponding artery, the pericardium, and the ventricular myocardium as landmarks.

Clinical trials evaluating percutaneous myoblast transplantation performed as a sole procedure in patients with post-infarction heart failure studied both endoventricular and transcoronary-venous catheter systems.

In 2003, the Rotterdam group[29] injected autologous myoblast suspensions into the area of post-infarction injury of five patients using an endoventricular catheter under electromagnetic guidance (*Figure 6*). Although the small sample size evidently precludes any conclusions about efficacy, this early experience has primarily documented the feasibility of this approach. An increase of LVEF and regional wall motion was observed at 3-month follow-up by angiography, though nuclear radiography and MRI failed to confirm this improvement. At 6 months, a trend towards increased LVEF was observed by both angiography and nuclear scan. A sub-study conducted to evaluate short- and long-term results of

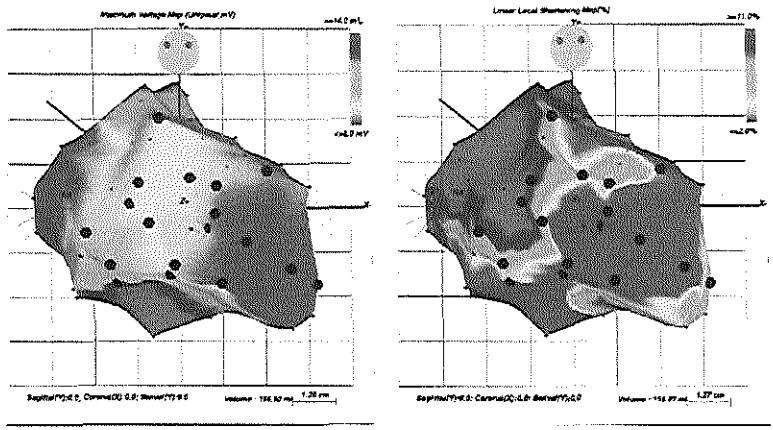


Figure 6 Unipolar voltage (left) and linear local shortening (right) NOGA maps. The myocardial scar is scaled red indicating an area with a <6 mV voltage and a <2% shortening. Black dots indicate the transendocardial injection sites.

myoblast transplantation on regional and global LV functional by two-dimensional echocardiography with dobutamine infusion and tissue Doppler imaging (TDI) showed an improvement of target wall systolic velocity and of global LV function during low-dose dobutamine infusion, indicating an improvement of contractile reserve.[44] (*Figure 7*).

In a recent study published by the same group, 10 to 15 injections of autologous myoblasts using Myostar™ (Cordis, Warren, NJ, USA) were given using an endoventricular approach. At 6-month follow-up, an increased EF and cardiac output, a reduction of 'systolic volume, and a trend towards improved stroke work were observed. These haemodynamic improvements were confirmed by pressure–volume loops analysis 1 year after percutaneous myoblast transplantation.[45] (*Figure 8*).

Another recently published study describes the results of transventricular injections using the fluoroscopy-guided MyoCath™ catheter (Bioheart, Weston, FL, USA) or the NOGA™-guided catheter system (Biosense-Webster, Waterloo, Belgium). The study failed to show improvement in the EF but wall motion score index improved both at rest and under low-dose dobutamine.[46]

A third catheter-based study, the POZNAN trial, was recently published by Siminiak *et al.*[33] This study was performed as a phase-one clinical trial to assess the safety and feasibility of both the TransAccess® catheter system and the percutaneous autologous myoblast transplantation performed as a sole therapy. Two to four intramyocardial injections delivered up to 100 million cells in 0.6–2.5 mL of saline solution to each patient. The trial confirmed the feasibility of intramyocardial injections using the TransAccess® system with an extremely precise advancement of the micro-lumen catheter in the remote target area up to 4 cm deep within the injured myocardium. The procedure was reported to be technically successful in all but one patient and did not cause any periprocedural adverse event.

The use of both the anterior interventricular vein and the middle cardiac vein, parallel to the posterior descending coronary artery, were shown to be feasible. In addition, compared with the anterior interventricular venous approach, in the POZNAN trial, a middle vein approach to advance the TransAccess® system succeeded in getting closer to the apical segments of the left ventricle.[33] The lack of procedural success in one patient, related to the inability to appropriately position the guiding catheter across the venous valve at the bifurcation of the great cardiac vein, suggests the need for a new and refined guiding catheter.

At 6-month follow-up, NYHA class improved in all patients and EF, assessed by echocardiography, significantly increased by 3 to 8 percentage points in six out of nine patients.[12,14]

Again, efficacy data, although considered promising, have to be interpreted cautiously because of the small size of the sample. These results, however, confirm previous laboratory findings in which autologous myoblasts delivered through the coronary sinus route significantly improved regional wall motion and global LV function.[47]

Safety issues related to myoblast transplantation

It may be speculated that the inability of skeletal myoblasts to transdifferentiate to cardiomyocytes and to form junctions with neighbouring cells may be a substrate for ventricular re-entry arrhythmia. Current experimental and clinical data indeed suggest a possibility of increased risk of arrhythmogenicity. In the first clinical series published by Menasché *et al.*,[8] four patients who underwent autologous skeletal myoblast transplantations during CABG received an implanted automatic internal cardioverter-defibrillators (AICD) due to sustained episodes of ventricular tachycardia (VT). In the Poznan CABG phase-one experience,[35] episodes of sustained

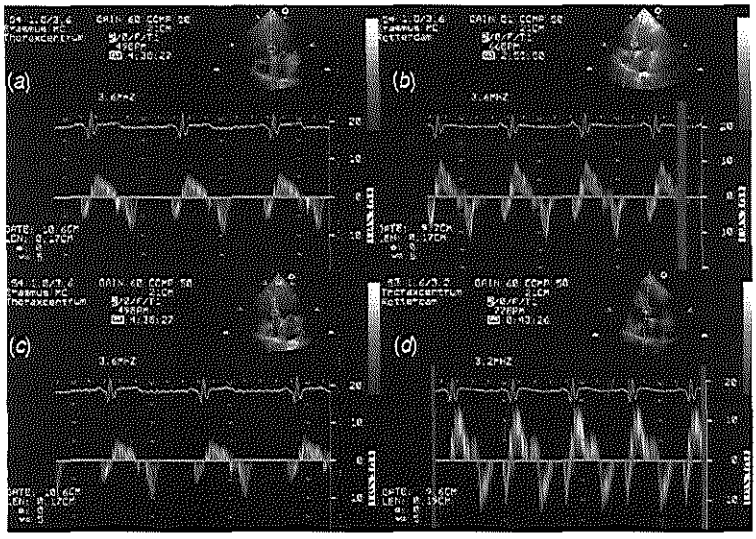


Figure 7 A significant increase of peak systolic velocity measured by TDI is shown at baseline (upper part) and at 1-year follow-up (lower part) both at rest (*A* and *C*) and after a low-dose dobutamine stress echocardiography (*B* and *D*).

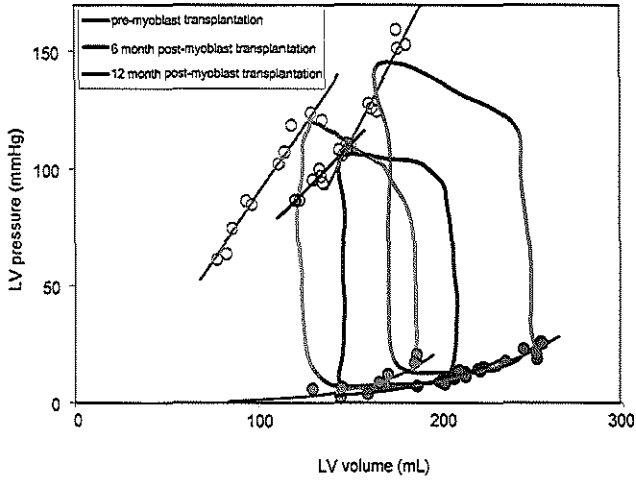


Figure 8 PV loops at baseline, 6 months and 12 months after myoblast transplantation. A significant increase in stroke volume, contractility (represented by ESPVR increased slope and leftward shift) and of diastolic stiffness (represented by upward shift and steeper EDPVR) is shown both at 6 and 12 months.

ventricular tachycardia (VT) were observed in first two patients during early post-operative period, but prophylactic amiodarone administration in the other patients prevented VT episodes so that no anti-arrhythmic treatment was continued later then 6 weeks during follow-up. In the MAGIC trial, designed by Menasché *et al.*, all the 97 treated patients received an AICD after cell transplantation: the trial was suspended in February 2006 after 120 patients were enrolled and the assessment of the risk/benefit ratio is currently under way.

The possible arrhythmogenic effect has been also noticed in trials using an endoventricular catheter-based approach. In the study conducted by Smits *et al.*,[46] one patient received an AICD 6 weeks after the myoblast injection and more seriously, two sudden deaths occurred, triggering the study steering committee to

consult the independent data safety monitoring board. The trial was temporarily suspended and resumed after having implemented the safety measures. Observations from percutaneous series in the POZNAN trial[43] indicate successful prevention of cell transplantation-related ventricular arrhythmias by prophylactic amiodarone administration, suggesting that AICD implantations are not necessarily needed in all patients who undergo myoblast transplantations.[48]

In the absence of electromechanical coupling, the arrhythmogenic mechanisms remain unclear. One possible explanation is that myoblasts, having the ability to generate burst of action potentials, may induce ventricular extrasystoles through electrotonic interactions.[49] Moreover, an arrhythmogenic role could be related to the procedure in itself, including myocardial puncture, inflammatory response to transplanted cells and immune reactions[49] rather than to possible problems with electromechanical coupling between newly developed myocytes and cardiomyocytes.

At the current stage, with only a small number of patients having undergone autologous skeletal myoblast transplantations, it is difficult to predict whether skeletal myoblasts are really arrhythmogenic, especially because patients with ischaemic LV dysfunction easily develop ventricular arrhythmia. Nevertheless, future studies on cell transplantation in patients with post-infarction heart failure will have to focus on potential arrhythmogenic effect. Similarly, large phase-two/three clinical trials are needed to assess the efficacy of myoblast transplantation in chronic post-infarction myocardial injury.

Conflict of interest: none declared.

References

1. Menasche P. Cell transplantation in myocardium. *Ann Thorac Surg* 2003;75(Suppl. 6):S20–S28.
2. Siminiak T, Kurpisz M. Myocardial replacement therapy. *Circulation* 2003;108:1167–1171.
3. Dimmeler S, Zeiher AM. Wanted! The best cell for cardiac regeneration. *J Am Coll Cardiol* 2004;44:464–466.
4. Dimmeler S, Zeiher AM, Schneider MD. Unchain my heart: the scientific foundations of cardiac repair. *J Clin Invest* 2005;115:572–583.
5. Laflamme MA, Murry CE. Regenerating the heart. *Nat Biotechnol* 2005;23:845–856.
6. Rafii S, Lyden D. Therapeutic stem and progenitor cell transplantation for organ vascularization and regeneration. *Nat Med* 2003;9:702–712.
7. Edelberg JM, Xaymardan M, Rafii S, Hong MK. Adult cardiac stem cells—where do we go from here? *Sci Aging Knowledge Environ* 2003;2003:PE17.
8. Menasche P, Hagege AA, Vilquin JT, Desnos M, Abergel E, Pouzet B, Bel A, Sarateanu S, Scorsin M, Schwartz K, Bruneval P, Benbunan M, Marolleau JP, Duboc D. Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction. *J Am Coll Cardiol* 2003;41:1078–1083.
9. Pagani FD, DerSimonian H, Zawadzka A, Wetzel K, Edge AS, Jacoby DB, Dinsmore JH, Wright S, Aretz TH, Eisen HJ, Aaronson KD. Autologous skeletal myoblasts transplanted to ischemia-damaged myocardium in humans. Histological analysis of cell survival and differentiation. *J Am Coll Cardiol* 2003;41:879–888.
10. Leobon B, Garcin I, Menasche P, Vilquin JT, Audinat E, Charpak S. Myoblasts transplanted into rat infarcted myocardium are functionally isolated from their host. *Proc Natl Acad Sci USA* 2003;100:7808–7811.
11. Ghostine S, Carrion C, Souza LC, Richard P, Bruneval P, Vilquin JT, Pouzet B, Schwartz K, Menasche P, Hagege AA. Long-term efficacy of myoblast transplantation on regional structure and function after myocardial infarction. *Circulation* 2002;106(Suppl. 1):I131–I136.
12. Reinecke H, Murry CE. Transmural replacement of myocardium after skeletal myoblast grafting into the heart. Too much of a good thing? *Cardiovasc Pathol* 2000;9:337–344.
13. Reinecke H, Minami E, Virag JI, Murry CE. Gene transfer of connexin43 into skeletal muscle. *Hum Gene Ther* 2004;15:627–636.
14. Beyer EC, Paul DL. *J Cell Biol* 1987;105:2621–2629.
15. Tolmachov O, Ma YL, Themis M, Patel P, Spohr H, Macleod KT, Ullrich ND, Kienast Y, Coutelle C, Peters NS. Overexpression of connexin 43 using a retroviral vector improves electrical coupling of skeletal myoblasts with cardiac myocytes *in vitro*. *BMC Cardiovasc Disord* 2006;6:25.
16. Rubart M, Soonpaa MH, Nakajima H, Field LJ. Spontaneous and evoked intracellular calcium transients in donor-derived myocytes following intracardiac myoblast transplantation. *J Clin Invest* 2004;114:775–783.
17. Taylor DA, Atkins BZ, Hungspreugs P, Jones TR, Reedy MC, Hutcheson KA, Glower DD, Kraus WE. Regenerating functional myocardium: improved performance after skeletal myoblast transplantation. *Nat Med* 1998;4:929–933.
18. Hagege AA, Vilquin JT, Bruneval P, Menasche P. Regeneration of the myocardium: a new role in the treatment of ischaemic heart disease? *Hypertension* 2001;38:1413–1415.
19. Scorsin M, Hagege A, Vilquin JT, Fiszman M, Marotte F, Samuel JL, Rappaport L, Schwartz K, Menasche P. Comparison of the effects of fetal cardiomyocyte and skeletal myoblast transplantation on postinfarction left ventricular function. *J Thorac Cardiovasc Surg* 2000;119:1169–1175.
20. Ravens U. Electrophysiological properties of stem cells. *Herz* 2006;31:123–126.
21. Reinecke H, Zhang M, Bartosek T, Murry CE. Electromechanical coupling between skeletal and cardiac muscle. Implications for infarct repair. *J Cell Biol* 2000;149:731–740.
22. Tambara K, Sakakibara Y, Sakaguchi G, Lu F, Premaratne GU, Lin X, Nishimura K, Komeda M. Transplanted skeletal myoblasts can fully replace the infarcted myocardium when they survive in the host in large numbers. *Circulation* 2003;108(Suppl. 1):II259–II263.
23. Jain M, DerSimonian H, Brenner DA, Ngoy S, Teller P, Edge AS, Zawadzka A, Wetzel K, Sawyer DB, Colucci WS, Apstein CS, Liao R. Cell therapy attenuates deleterious ventricular remodeling and improves cardiac performance after myocardial infarction. *Circulation* 2001;103:1920–1927.
24. McConnell PI, del Rio CL, Jacoby DB, Pavlicova M, Kwiatkowski P, Zawadzka A, Dinsmore JH, Astra L, Wisel S, Michler RE. Correlation of autologous skeletal myoblast survival with changes in left ventricular remodeling in dilated ischaemic heart failure. *J Thorac Cardiovasc Surg* 2005;130:1001.
25. Zhang FB, Yang HT. Plasticity of bone marrow mesenchymal stem cells differentiating into cardiomyocytes and the potential of cardiac therapeutics. *Sheng Li Ke Xue Jin Zhan* 2006;37:199–204.
26. Xia JH, Xie AN, Zhang KL, Xu L, Zheng XY. The vascular endothelial growth factor expression and vascular regeneration in infarcted myocardium by skeletal muscle satellite cells. *Chin Med J (Engl)* 2006;119:117–121.
27. Hill E, Boontheekul T, Mooney DJ. Regulating activation of transplanted cells controls tissue regeneration. *Proc Natl Acad Sci USA* 2006;103:2494–2499.
28. Murtuza B, Suzuki K, Bou-Gharios G, Beauchamp JR, Smolenski RT, Partridge TA, Yacoub MH. Transplantation of skeletal myoblasts secreting an IL-1 inhibitor modulates adverse remodeling in infarcted murine myocardium. *Proc Natl Acad Sci USA* 2004;101:4216–4221.
29. Smits PC, van Geuns RJ, Poldermans D, Bountioukos M, Onderwater EE, Lee CH, Maat AP, Serruys PW. Catheter-based intramyocardial injection of autologous skeletal myoblasts as a primary treatment of ischaemic heart failure: clinical experience with six-month follow-up. *J Am Coll Cardiol* 2003;42:2063–2069.
30. Herreros J, Prosper F, Perez A, Gavira JJ, Garcia-Velloso MJ, Barba J, Sanchez PL, Canizo C, Rabago G, Marti-Climent JM, Hernandez M,

Lopez-Holgado N, Gonzales-Santos JM, Martin-Luengo C, Alegria E. Autologous intramyocardial injection of cultured skeletal muscle-derived stem cells in patients with non-acute myocardial infarction. *Eur Heart J* 2003;24:2012–2020.
31. Siminiak T, Kalawski R, Fiszer D, Jerzykowska O, Rzeznicczak J, Rozwadowska N, Kurpisz M. Autologous skeletal myoblast transplantation for the treatment of postinfarction myocardial injury: phase I clinical study with 12 months of follow-up. *Am Heart J* 2004;148: 531–537.
32. Chachques JC, Herreros J, Trainini J, Juffe A, Rendal E, Prosper F, Genovese J. Autologous human serum for cell culture avoids the implantation of cardioverter-defibrillators in cellular cardiomyoplasty. *Int J Cardiol* 2004;95(Suppl. 1):S29–S33.
33. Siminiak T, Fiszer D, Jerzykowska O, Grygielska B, Rozwadowska N, Kalmucki P, Kurpisz M. Percutaneous trans-coronary-venous transplantation of autologous skeletal myoblasts in the treatment of post-infarction myocardial contractility impairment: the POZNAN trial. *Eur Heart J* 2005;26:1188–1195.
34. Menasche P, Hagege A, Scorsin M, Pouzet B, Desnos M, Duboc D, Schwartz K, Vilquin JT, Marolleau JP. Autologous skeletal myoblast transplantation for cardiac insufficiency. First clinical case. *Arch Mal Coeur Vaiss* 2001;94:180–182.
35. Siminiak T, Kalawski R, Kurpisz M. Myoblast transplantation in the treatment of postinfarction myocardial contractility impairment. *Kardiol Pol* 2002;56/2:131–137.
36. Dib N, McCarthy P, Campbell A, Yeager M, Pagani FD, Wright S, MacLellan WR, Fonarow G, Eisen HJ, Michler RE, Binkley P, Buchele D, Korn R, Ghazoul M, Dinsmore J, Opie SR, Diethrich E. Feasibility and safety of autologous myoblast transplantation in patients with ischaemic cardiomyopathy. *Cell Transplant* 2005;14: 11–19.
37. Dib N, Michler RE, Pagani FD, Wright S, Kereiakes DJ, Lengerich R, Binkley P, Buchele D, Anand I, Swingen C, DiCarli MF, Thomas JD, Jaber WA, Opie SR, Campbell A, McCarthy P, Yeager M, Dilsizian V, Griffith BP, Korn R, Kreuger SK, Ghazoul M, MacLellan WR, Fonarow G, Eisen HJ, Dinsmore J, Diethrich E. Safety and feasibility of autologous myoblast transplantation in patients with ischaemic cardiomyopathy: four-year follow-up. *Circulation* 2005;112: 1748–1755.
38. Muller-Ehmsen J, Whittaker P, Kloner RA, Dow JS, Sakoda T, Long TI, Laird PW, Kedes L. Survival and development of neonatal rat cardiomyocytes transplanted into adult myocardium. *J Mol Cell Cardiol* 2002;34:107–116.
39. Siminiak T, Fiszer D, Jerzykowska O, Grygielska B, Kalmucki P, Kurpisz M. Percutaneous autologous myoblast transplantation in the treatment of post-infarction myocardial contractility impairment–report on two cases. *Kardiol Pol* 2003;59:492–501.
40. Fuchs S, Satler LF, Kornowski R, Okubagzi P, Weisz G, Baffour R, Waksman R, Weissman NJ, Cerqueira M, Leon MB, Epstein SE. Catheter-based autologous bone marrow myocardial injection in no-option patients with advanced coronary artery disease: a feasibility study. *J Am Coll Cardiol* 2003;41:1721–1724.
41. Perin EC, Dohmann HF, Borojevic R, Silva SA, Sousa AL, Mesquita CT, Rossi MI, Carvalho AC, Dutra HS, Dohmann HJ, Silva GV, Belem L, Vivacqua R, Rangel FO, Esporcatte R, Geng YJ, Vaughn WK, Assad JA, Mesquita ET, Willerson JT. Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischaemic heart failure. *Circulation* 2003;107:2294–2302.
42. Sarmento-Leite R, Silva GV, Dohman HF, Rocha RM, Dohman HJ, de Mattos ND, Carvalho LA, Gottechall CA, Perin EC. Comparison of left ventricular electromechanical mapping and left ventricular angiography: defining practical standards for analysis of NOGA maps. *Tex Heart Inst J* 2003;30:19–26.
43. Siminiak T, Fiszer D, Jerzykowska O, Grygielska B, Rozwadowska N, Kalmucki P, Kurpisz M. Percutaneous transvenous transplantation of autologous myoblasts in the treatment of postinfarction heart failure: the POZNAN trial. *Eur Heart J* 2004;25(Suppl.):264.
44. Biagini E, Valgimigli M, Smits PC, Poldermans D, Schinkel AF, Rizzello V, Onderwater EE, Bountioukos M, Serruys PW. Stress and tissue Doppler echocardiographic evidence of effectiveness of myoblast transplantation in patients with ischaemic heart failure. *Eur J Heart Fail* 2006;8:641–648.
45. Steendijk P, Smits PC, Valgimigli M, van der Giessen WJ, Onderwater EE, Serruys PW. Intramyocardial injection of skeletal myoblasts: long-term follow-up with pressure-volume loops. *Nat Clin Pract Cardiovasc Med* 2006;3(Suppl. 1):S94–S100.
46. Smits PC, Mienaber C, Colombo A, Ince H, Carlino M, Theuns D, Biagini E, Valgimigli M, Onderwater E, Steendijk P, Peters NS, Goedhart D, Serruys PW. Myocardial repair by percutaneous cell transplantation of autologous skeletal myoblast as a stand alone procedure in post myocardial infarction chronic heart failure patients. *Eurointervention* 2006;1:417–424.
47. Brasselet C, Morichetti MC, Messas E, Carrion C, Bissery A, Bruneval P, Vilquin JT, Lafont A, Hagege AA, Menasche P, Desnos M. Skeletal myoblast transplantation through a catheter-based coronary sinus approach: an effective means of improving function of infarcted myocardium. *Eur Heart J* 2005;26:1551–1556.
48. Abraham MR, Hare JM. Is skeletal myoblast transplantation pro-arrhythmic? The jury is still out. *Heart Rhythm* 2006;3:462–463.
49. Makkar RR, Lill M, Chen PS. Stem cell therapy for myocardial repair: is it arrhythmogenic? *J Am Coll Cardiol* 2003;42:2070–2072.

CHAPTER 24

RATIONALE AND INTERIM ANALYSIS DATA FROM THE SEISMIC STUDY

Clinical status and controversies

EuroIntervention

Rationale and interim analysis data from the SEISMIC study

E. Meliga[1,2], MD; H.J. Duckers[1], MD, PhD; R. Spencer[3]; P.W. Serruys[1]*, MD, PhD; on behalf of the SEISMIC Investigators

1. Thoraxcenter, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands; 2. Interventional Cardiology Department, S. Giovanni Battista Hospital, University of Turin, Italy; 3. Bioheart Inc., Sunrise, FL, USA

R. Spencer is an employee of Bioheart Inc. The SEISMIC investigators and study sites appear in the appendix.

The study was sponsored by Bioheart Inc. The other authors have no conflict of interest to declare.

Introduction

Cardiovascular disease continues to be a major health epidemic throughout the world and is the leading cause of morbidity and mortality in the Western world, with its prevalence constantly increasing in developing countries. At present, coronary artery disease, including post-infarction chronic heart failure, accounts for over 7 million deaths per year (over 2 million in Europe alone), and this number is expected to nearly double in the next 20 years[1,2].

These facts clearly illustrate the need for improvement in the revascularisation and medical therapies currently available, as well as for the development of novel therapies capable of preventing or reversing negative remodelling and even regenerating failing myocardium. In the last 10 years, repair of cardiac muscle by stem cells in patients with post-ischaemic chronic heart failure has been tested in several preclinical and phase I-II clinical studies utilising different cell types and means of delivery[3-10].

Although almost all of these studies achieved promising results both in terms of safety and efficacy, few direct clinical side-by-side comparisons have been performed, and thus the quest for the ideal cell type is still ongoing. Several preclinical studies have recently been performed to compare the beneficial effects of different cell types for cellular cardiomyoplasty (Table 1). According to these preclinical studies, in the sub-acute or chronic MI setting, skeletal myoblast transplantation may be more effective than transplantation of bone marrow mononuclear cells, dermal fibroblasts, cardiac fibroblasts or adult cardiomyocytes[11-14].

These results may be related to the superior degree to which myoblasts exhibit resistance to ischaemia as compared with cardiocytes. Further, myoblasts appear to have a noticeable impact on cardiac systolic function as compared with the passive effects of fibroblasts and other cell types on cardiac compliance[15]. To date, the feasibility of myoblasts for the treatment of CHF has been confirmed in several clinical trials in which autologous skeletal myoblasts were implanted either during open-chest surgery[16-19] or via percutaneous delivery[8,9,20] as a stand alone procedure (Table 2). These encouraging results have led to the design of new myoblast transplantation protocols, which are currently under investigation in ongoing clinical studies and which we hope will impart a clearer understanding of their applicability in future clinical practice.

The SEISMIC study: rationale and description

Rationale

Previous data derived from pre-clinical studies demonstrated that the implantation of autologous skeletal myoblasts may lead to replacement of non-functioning myocardial scar with functional contractile tissue and consistent improvement in global LVEF, regional wall motion and viability. Results from phase I-II clinical trials suggest skeletal myoblast implantation at the time of CABG may lead to similar effects, as do recent studies using percutaneous delivery as a stand-alone procedure. For these reasons autologous skeletal myoblast (MyoCell™) implantation using the MyoCath®

* *Corresponding author: Thoraxcenter, Erasmus University Medical Center, Rotterdam, PO Box 2040, 3000CA Rotterdam, The Netherlands. E-mail: p.w.j.c.serruys@erasmusmc.nl*

Table 1. Preclinical studies comparing skeletal myoblasts (SKMyo) with other cell types implantation.

Study	Species	Cell type	Outcome
Hutcheson et al[11]	Rabbit	SKMyo vs. FB	SKMyo superior to FB. SKMB improve both systolic and diastolic function. FB only improves diastolic
Horackova et al[12]	Pig	SKMyo vs. Cardiac FB vs. CardioMyo	Myotube formation in SKMyo treated animals, SKMyo superior to CardioMyo and Cardiac FB regarding remodelling; functional improvement in SKMyo treated animals
Agbulut et al[14]	Rat	SKMyo vs. AC133+	Myotubes in SKMyo treated group, No difference regarding LV function
Ott et al[13]	Rat	SKMyo vs.BMMCs	SKMyo superior to BMMCs regarding LV function

FB = fibroblasts; CardioMyo = cardiomyocites; BMMCs = bone marrow mononucleated cells; LV = left ventricle

Table 2. Comparison of clinical studies using myoblasts for post-infarction chronic heart failure.

Study	Cell type	Patients treated (n)	LVEF	Route of delivery	Results
Menasche et al[17]	SKMyo	10	24±4%	transepicardial	↑ global LVEF
Herreros et al[18]	SKMyo	11	36±8%	transepicardial	↑ global LVEF, ↑ regional wall motion and ↑ viability
Siminiak et al[19]	SKMyo	10	25-40%	transepicardial	↑ global LVEF, ↑ regional wall motion
Chachques et al[16]	SKMyo	20	28±3%	transepicardial	↑ global LVEF, ↑ regional wall motion and ↑ viability
Smits et al[9]	SKMyo	5	36±11%	transendocardial – NOGA guided	↑ global LVEF, ↑ regional wall motion
Siminiak et al[8]	SKMyo	9	30-49%	trans-coronary-venous	↑ global LVEF
Smits et al[20]	SKMyo	15	34±10%	transendocardial – NOGA guided	↑ regional wall motion, NYHA class improvement

SKMyo = skeletal myoblasts; NOGA = non-fluoroscopic electromechanical mapping; LVEF = left ventricle ejection fraction; NYHA = New York Heart Association

endoventricular catheter delivery system is being evaluated in this randomised, controlled study to explore the feasibility these cells may provide in adding a new dimension to the interventional management of post-infarct deterioration of cardiac function in patients with congestive heart failure.

MyoCell™

MyoCell™ is a proprietary technology of Bioheart Incorporated (Sunrise, FL, USA) and is composed of autologous skeletal myoblasts expanded *ex vivo* from an individual patient's skeletal striated muscle biopsy. Autologous skeletal myoblasts are isolated and subsequently expanded from approximately 10 grams of a skeletal muscle biopsy via a proprietary cell culturing process. Harvest is by trypsinisation, cell collection, and repeated washing with a commercially available transport medium to ensure removal of any residual serum from culturing. Following final re-suspension in transport medium, release testing is conducted and MyoCell™ is packaged and labelled for return shipment to the patient's treating physician for intramyocardial implantation. MyoCell™ has been previously delivered endovascularly via specifically designed percutaneous catheter delivery systems (MyoCath®, MyoStar® and TransAccess®). In the SEISMIC study, MyoCell™ is injected into the region of akinetic myocardial scar resulting from prior infarction. Multiple injections, each containing 0.5 mL of cell suspension (25×10^6 cells/mL) and spaced approximately 1cm apart, are performed to deliver MyoCell™ to the target region. The intended dose of MyoCell™ for each patient is between 150 and 800×10^6 cells. The maximum number of injections for each implantation procedure is 32 and the maximum number of cells injected is 800×10^6.

MyoCath®

The Bioheart MyoCath® catheter (Figure 1) is a 115 cm long, 8 Fr needle injection catheter with a deflectable tip and extendable 25 G stainless steel needle. A deflection knob and needle advancement control trigger are used (Figure 2) to manoeuvre the tip, advance the needle and control the needle depth.

During the procedure, a small incision is made in the patient's groin to provide arterial access in customary fashion. The catheter is advanced through an arterial femoral sheath retrograde across the aortic valve and into the left ventricular cavity. The injection tip of the MyoCath® is then positioned to the desired injection site of the left ventricle (via fluoroscopic guidance). The needle is advanced to a pre-set length by depressing the needle advance/retraction control, causing the needle to penetrate the target tissue to the pre-set depth. The attached syringe is then depressed to deliver the therapeutic dose (0.5 mL/per injection) to the injection site. After injection, the needle is retracted, the tip is repositioned, and another injection is made. Subsequent injections, approximately 1 cm apart, are made to all desired areas affected by prior infarct to complete the cellular cardiomyoplasty procedure.

The Bioheart MyoCath® delivery system has been used in more than 50 patients and three clinical studies worldwide without note of any serious adverse clinical events during the implantation procedure.

Study design

The SEISMIC Trial (Safety and Effects of Implanted [Autologous] Skeletal Myoblasts [MyoCell™] using an Injection Catheter) is a phase II, open-label, randomised, multicentre study designed to assess the safety and cardiovascular effects of myogenic muscle stem cells, as delivered by the MyoCath®, in congestive heart failure patients post myocardial infarction(s). Forty-six patients were targeted for enrolment at 12 study centres throughout Europe, with two-thirds of the patients randomised to the MyoCell™ treatment arm, and the other third randomised to the control arm (and receiving standard medical therapy only).

Here we report the DSMB interim analysis of the first 25 randomised patients.

Enrolment was completed in the beginning of 2007. Per protocol, all eligible patients experienced a Q-wave myocardial infarction at least 90 days prior to the surgical muscle biopsy resulting in a large area of akinesia (as confirmed by angiography and echocardiography) and residual global left ventricular ejection fraction at screening of ≥ 20% and ≤ 45% (as assessed by MUGA scan). Functional class was NYHA II or III without requirement, or indication for revascularisation (ruled out by angiography or dobutamine stress scintigraphy). Optimal medical therapy was to have been initiated at least 2 months prior to study entry, and all patients enrolled must have been fitted with an ICD (single-lead) at least 6 months prior to enrolment in the protocol. All randomised patients were initiated on anti-arrhythmic therapy (amiodarone) at screening, for at least one month pre- and post- procedure; both groups were followed for 6 months and evaluations were done at baseline, 1 month, 3 months and 6 months by office visits as well as by laboratory and instrument tests (ECG, echocardiography, dynamic ECG-Holter and MUGA scan at 6-month FU).

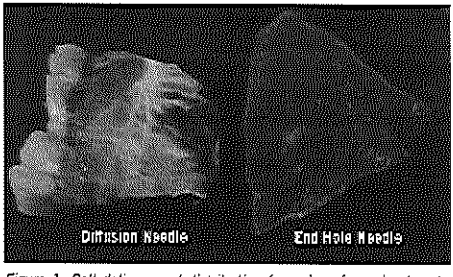


Figure 1. Cell delivery and distribution (green) performed using the new tip-closed with side holes Myocath (on the left) and the old tip with single end-hole catheter (on the right).

The primary safety endpoint of the study is the observed number of serious adverse events (SAE) in the treatment arm vs. control arm at 3 and 6 months, while the primary efficacy endpoint is observed improvement in LVEF (as measured by MUGA) at 3 and 6 months vs. baseline for both the treatment and control arms. Additional secondary endpoints include improvement in 6-minute walk time, NYHA classification, QOL score (Minnesota), global and regional contractility, wall thickness, coronary perfusion and changes in overall infarct size at 3 and 6 months vs. baseline. SAEs were defined by the study protocol as any adverse event deemed fatal, life-threatening, requiring unexpected hospitalisation or resulting in permanent impairment, as well as any events which the investigator deemed jeopardising toward the patient.

Preliminary safety data

Safety data was available in December 2006 on 25 of the 46 randomised patients (16 treated with Myocell™, 9 controls), with a minimum follow-up period of 30-days for all patients evaluated. At baseline, treated patients on average experienced their last MI 9.3±5 years prior to screening (range 2-21), while control patients on average were 7.1±4 years removed from their last MI (range 2-16). Ten treated patients had documented prior history of VT (63%) while 6 control patients had experienced prior VT (67%). In the treatment arm, mean LVEF was 30.0%±10.4%, with 8 patients (50%) NYHA Class III, while control arm patients entered with a mean LVEF of 32.8%±11.1%, with 3 patients (33%) NYHA Class III. On average, treated patients provided 7.9±4 grams of muscle tissue and were injected with 598±110x10^6 cells over 24±4 injections. All patients were treated with cells ≥ 50% positive for CD56 staining.

Twelve non-hierarchical serious adverse events (Table 3) occurred in the treatment group in 6 of 16 patients: 1 death (due to multi organ failure), 6 VT with appropriate ICD firing (5 deemed possibly related to cell therapy and all resolved), 1 case of worsening heart failure (patient recovered), 1 case of pericarditis (patient recov-

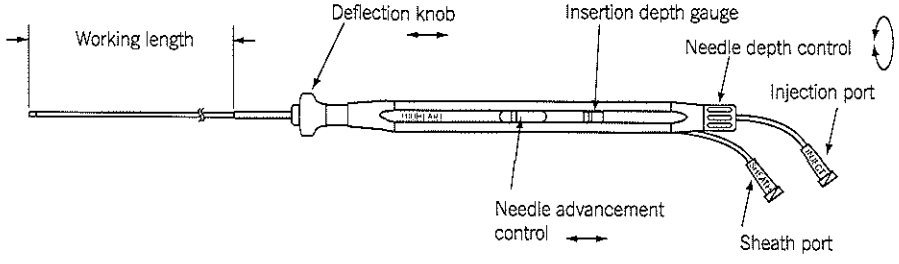


Figure 2. The Myocath™ hand piece.

Table 3. Description of arrhythmic Serious Adverse Events (SAE) occurred in the treatment arm.

SAE	Days after procedure	Outcome	Relationship
VT+ICD firing	5	Recovered	Probable to Myocell
VT+ICD firing	11	Recovered	Probable to Myocell
VT+ICD firing	12	Recovered	Probable to Myocell
VT+ICD firing	25	Recovered	Probable to Myocell
VT+ICD firing	8	Recovered	Probable to Myocell
VT+ICD firing	Prior to cell implantation	Recovered	Not related with Myocell
NSVT	7	Self resolving	Plausible to Myocell

VT = ventricular tachycardia; ICD = implantable cardioverter defibrillator; NSVT = non-sustained ventricular tachycardia

ered), 1 NSVT (self-resolving), 1 post-biopsy haematoma (resolved) and 1 report of herpes zoster (resolved). In the control arm, two non-hierarchical serious adverse events occurred in 2 of 9 patients: 1 non sustained VT and 1 diverticulitis, both which resolved.

Regarding the treated patients, VTs episodes with ICD firing occurred in 4 patients (2 patients with 2 events and 2 patient with 1 event each). One patient had two separate episodes at day 5 and 11 post transplantation and, after a period of clinical recovery, progressively declined and died of multiple organ failure approximately 30 days after the index procedure. The other multi-firing ICD patient experienced 2 separate firings at 12 and 25 days post transplantation, with complete recovery thereafter and no further reports of VT. The other 2 patients experiencing 1 event each both fully recovered, with no other VTs episodes were observed. One patient experienced appropriate ICD shock 8 days post implant, while the other patient experienced appropriate ICD shock prior to the cell implantation procedure. All arrhythmic events occurred within the first month following the transplantation procedure.

Of note, 3 of the 4 treated patients experiencing 6 VT events were confirmed non-compliant with prophylactic amiodarone use per protocol, and all 4 of these patients had documented prior history of VT with ICD firing prior to entering the study.

Preliminary efficacy data

Though the limited amount of data currently available does not allow for meaningful insight into the efficacy of the MyoCell therapy, preliminary trends appear encouraging.

Six-minute walk distance data available for 3 treatment group patients and 4 control group patients demonstrate six minute walk distance improved, on average, 97±51.4 meters as compared to an average decline of 20±147.1 meters experienced by the control group patients.

NYHA Class data available for 8 treatment group patients and 6 control group patients revealed that 37.5% of the treatment group patients improved by at least one NYHA Class at 3 months following treatment as compared to 0% of the control group patients.

50% of the treatment group patients improved by at least one NYHA Class at 6 months following treatment as compared to 25% percent of the control group patients who improved.

None of the treatment group patients experienced a decline in NYHA Class at either 3 or 6 months following treatment.

LVEF as assessed by MUGA also showed a trend in improvement for the treatment group, with treated patients improving from 30.0 %±10.4% at baseline to 31.7%±21.8% at 6 months while control patients declined from 32.8%±11.1% to 31.7%±8.3% over the same time.

50% of treated patients experienced an improvement in LVEF while 57% of the control patients exhibited a reduction in LVEF.

Conclusions

Management of heart failure patients with advanced cardiomyopathy is a daunting task – patients often present with multiple medical conditions, a history of arrhythmia and little available in terms of alternative treatments to standard medical therapy. Novel therapies are needed to provide improved treatment options, and cell therapy is a promising start to this endeavour. Though complete efficacy data are not yet available and safety data are not yet fully adjudicated, these preliminary results suggest that myoblast therapy for CHF is largely safe and effective. Arrhythmic events are largely manageable with close observation and prophylactic use of ICDs and amiodarone therapy; when arrhythmic SAEs do occur, they typically appear during the first month following implantation and can largely be mitigated with appropriate medical management. Patients receiving myoblast-based cell therapy also tend to show improvement in quality of life and mechanical function over time, as evidenced in prior (completed) clinical studies and in the initial trends reported above. We look forward to receiving the final data in order to reach more definitive conclusions.

Appendix

The following investigators and institutions participated in the SEISMIC study: P.W. Serruys, Erasmus MC, Rotterdam, The Netherlands; J. Bartunek, OLV Ziekenhuis, Aalst, Belgium; V. Legrand, CHU de Liege Sart-Tilman, Liege, Belgium; W. Van Mieghem, ZOL Campus, St.Jan, Genk, Belgium; C. Nienaber, University Hospital Rostock, Germany; J. Schofer, Hamburg University Cardiovascular Center, Hamburg, Germany; C. Hehrlein, University of Freiburg, Germany; J. Waltenberger, University Hospital, Maastricht, The Netherlands; C. Macaya, Instituto Cardiovascular, Hospital Clinico San Carlos, Madrid, Spai; A. Gershlick, University of Leicester, Glenfield Hospital, Leicester, United Kingdom; N. Peters, St. Mary's Hospital and Imperial College, London, United Kingdom; T. Siminiak, Poznan University School of Medical Sciences, Poland; P. Smits, MCRZ, Rotterdam, The Netherlands.

References

1. Husten L. Global epidemic of cardiovascular disease predicted. *Lancet.* 1998;352:1530

2. Cohn JN, Francis GS. Cardiac failure: a revised paradigm. *J Card Fail.* 1995;1:261-6.

3. Assmus B, Schachinger V, Teupe C, Britten M, Lehmann R, Dobert N, Grunwald F, Aicher A, Urbich C, Martin H and others. Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI). *Circulation.* 2002;106(24):3009-17.

4. Wollert KC, Meyer GP, Lotz J, Ringes-Lichtenberg S, Lippolt P, Breidenbach C, Fichtner S, Korte T, Hornig B, Messinger D and others.

Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *Lancet.* 2004;364(9429):141-8.

5. Memon IA, Sawa Y, Miyagawa S, Taketani S, Matsuda H. Combined autologous cellular cardiomyoplasty with skeletal myoblasts and bone marrow cells in canine hearts for ischemic cardiomyopathy. *J Thorac Cardiovasc Surg.* 2005;130(3):646-53.

6. Dib N, Michler RE, Pagani FD, Wright S, Kerelakes DJ, Lengerich R, Binkley P, Buchele D, Anand I, Swingen C and others. Safety and feasibility of autologous myoblast transplantation in patients with ischemic cardiomyopathy: four-year follow-up. *Circulation.* 2005;112(12):1748-55.

7. Ince H, Petzsch M, Rehders TC, Chatterjee T, Nienaber CA. Transcatheter transplantation of autologous skeletal myoblasts in postinfarction patients with severe left ventricular dysfunction. *J Endovasc Ther.* 2004;11(6):695-704.

8. Siminiak T, Fiszer D, Jerzykowska O, Grygielska B, Rozwadowska N, Kalmucki P, Kurpisz M. Percutaneous trans-coronary-venous transplantation of autologous skeletal myoblasts in the treatment of post-infarction myocardial contractility impairment: the POZNAN trial. *Eur Heart J.* 2005;26(12):1188-95.

9. Smits PC, van Geuns RJ, Poldermans D, Bountioukos M, Onderwater EE, Lee CH, Maat AP, Serruys PW. Catheter-based intramyocardial injection of autologous skeletal myoblasts as a primary treatment of ischemic heart failure: clinical experience with six-month follow-up. *J Am Coll Cardiol.* 2003;42(12):2063-9.

10. Chen SL, Fang WW, Ye F, Liu YH, Qian J, Shan SJ, Zhang JJ, Chunhua RZ, Liao LM, Lin S and others. Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. *Am J Cardiol.* 2004;94(1):92-5.

11. Hutcheson KA, Atkins BZ, Hueman MT, Hopkins MB, Glower DD, Taylor DA. Comparison of benefits on myocardial performance of cellular cardiomyoplasty with skeletal myoblasts and fibroblasts. *Cell Transplant.* 2000;9(3):359-68.

12. Horackova M, Arora R, Chen R, Armour JA, Cattini PA, Livingston R, Byczko Z. Cell transplantation for treatment of acute myocardial infarction: unique capacity for repair by skeletal muscle satellite cells. *Am J Physiol Heart Circ Physiol.* 2004;287(4):H1599-608.

13. Ott HC, Bonaros N, Marksteiner R, Wolf D, Margreiter E, Schachner T, Laufer G, Hering S. Combined transplantation of skeletal myoblasts and bone marrow stem cells for myocardial repair in rats. *Eur J Cardiothorac Surg.* 2004;25(4):627-34.

14. Agbulut O, Vandervelde S, Al Attar N, Larghero J, Ghostine S, Leobon B, Robidel E, Borsani P, Le Lorc'h M, Bissery A and others. Comparison of human skeletal myoblasts and bone marrow-derived CD133+ progenitors for the repair of infarcted myocardium. *J Am Coll Cardiol.* 2004;44(2):458-63.

15. Kittleson MM, Minhas KM, Irizarry RA, Ye SQ, Edness G, Breton E, Conte JV, Tomaselli G, Garcia JG, Hare JM. Gene expression analysis of ischemic and nonischemic cardiomyopathy: shared and distinct genes in the development of heart failure. *Physiol Genomics.* 2005;21:299-307.

16. Chachques JC, Herreros J, Trainini J, Juffe A, Rendal E, Prosper F, Genovese J. Autologous human serum for cell culture avoids the implantation of cardioverter-defibrillators in cellular cardiomyoplasty. *Int J Cardiol.* 2004;95 Suppl 1:S29-33.

17. Menasche P. Myoblast-based cell transplantation. *Heart Fail Rev.* 2003;8(3):221-7.

18. Herreros J, Prosper F, Perez A, Gavira JJ, Garcia-Velloso MJ, Barba J, Sanchez PL, Canizo C, Rabago G, Marti-Climent JM and others. Autologous intramyocardial injection of cultured skeletal muscle-derived stem cells in patients with non-acute myocardial infarction. *Eur Heart J.* 2003;24(22):2012-20.

19. Siminiak T, Kalawski R, Fiszer D, Jerzykowska O, Rzeczniczak J, Rozwadowska N, Kurpisz M. Autologous skeletal myoblast transplantation for the treatment of postinfarction myocardial injury: phase I clinical study with 12 months of follow-up. *Am Heart J.* 2004;148(3):531-7.

20. Smits P, Nienaber C, Colombo A, Ince H, Carlino M, Theuns D, Biagini E, Valgimigli M, Onderwater E, Steendijk P, Peters N, Goedhart D, Serruys PW. Myocrdial repair by percutaneous cell transplantation of autologous skeletal myoblast as a stand alone procedure in post myocardial infarction chronic heart failure patients. *EIJ.* 2006:1:417-424.

CHAPTER 25

MAGNETICALLY SUPPORTED PROCEDURES AND CARDIAC REGENERATION

Delivery techniques and self imaging

EuroIntervention

Magnetically supported procedures and cardiac regeneration

Mark S. Patterson[1,2*], MSc, MRCP; Eric Duckers[1], MD, PhD; Steve Ramcharitar[1], MRCP DPhil; Emmanuelle Meliga[1], MD; Sander van Weenen[1], BSc; Anne-Marie Maugenest[1], RN; Emerson Perin[3], MD, PhD; Patrick W. Serruys[1], MD, PhD

1. Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands; 2. Amsterdam Department of Interventional Cardiology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands; 3. Texas Heart Institute, St Luke's Episcopal Hospital, Houston, Texas, USA

Mark Patterson has received speaker's fees from Stereotaxis, all other authors declare no conflict of interest.

Introduction

Cardiac failure secondary to ischaemic heart disease is a leading cause of morbidity and mortality[1]. Infarction leads to cell loss by oxidative stress and reperfusion injury. Chronic ischaemia and myocyte loss produces progressive expansion of the infarct area, fibrous replacement of the myocardium and predisposes to dilation of the left ventricle[2], a major factor in survival[3]. Progenitor/stem cell therapy has potential for promoting structural and functional repair of the myocardium.

Progenitor/stem cells may stimulate either angiogenesis[4,5] by the release of growth factors and anti-apoptotic factors (including Akt, VEGF and FGF), and/or vasodilation (by VEGF) with an increase in INOS bioavailability that may help maintain cell viability and encourage blood flow. More controversially, progenitor/stem cells from the bone marrow, circulating blood or embryonically-derived, may lead to myocardial cell regeneration[6,7]. However to date, improvements in cardiac function and structure have been modest[8,9].

Current delivery techniques include 2-D angiographically guided endocardial injection and catheter based intracoronary release. However, these techniques have general limitations that include imprecise on-table identification of the best areas to target, poor ability in targeting a specific area, and mediocre identification of the treated area at follow-up. In addition, intracoronary release has specific drawbacks such as induction of ischaemia, or the 'shedding' of cells into the general circulation. Two particular clinical settings that appear particularly appropriate for progenitor/stem cell therapy are those of recent anterior myocardial infarction that results in reduced LV function and of chronic, ischaemic, dilated cardiomyopathy. The development and integration of electromechanical mapping technology, NOGA® XP (Biologics Delivery Systems™, Cordis Corporation, Diamond Bar, CA, USA) with the development of a magnetically navigable injection catheter, the MyoStar™ injection catheter (Biologics Delivery Systems™), could transform cell delivery.

This article will review the principles of magnetic navigation with the forthcoming technology; consider how localisation, delivery and follow-up might potentially be improved compared with current techniques; discuss the relevance to two of the clinical settings that might derive the most benefit; and mention the possibilities of improved percutaneous revascularisation that might be used to optimise the local milieu for progenitor/stem cell survival. The purpose of this article is to suggest and speculate upon how this technology might allow integration of the real-time visualisation

* *Corresponding author: Amsterdam Department of Interventional Cardiology, OLVG, 1e Oosterparkstraat 279, 1090 HM, Amsterdam, The Netherlands. E-mail: markspatterson@doctors.net.uk*

of target tissue with site directed deliverability in order to reduce procedure times and irradiation, and to simultaneously improve efficacy and follow-up.

Magnetic navigation system

The magnetic navigation system (Niobe®, Stereotaxis, St. Louis, MO, USA) consists of two adjustable permanent magnets on either side of the fluoroscopy table (see Figure 1).

In essence the system does three things. Firstly, the system operates using a 3-D reconstruction that is either produced from angiographic images (as in the case of coronary arteries) or, alternatively, an imported 3-D reconstruction from an external system e.g. NOGA® XP. Secondly, the spatial orientation and location of this reconstruction is matched to the real-life patient's internal cardiac anatomy; i.e. coronary artery or cardiac chamber. Thirdly, the model gives the real-time, on-line vectors to direct an external magnetic field to orientate a magnet on an intravascular device to match the direction required for navigation through the 3-D reconstruction. The result is the ability to use 3-D information in real-time in patient therapy.

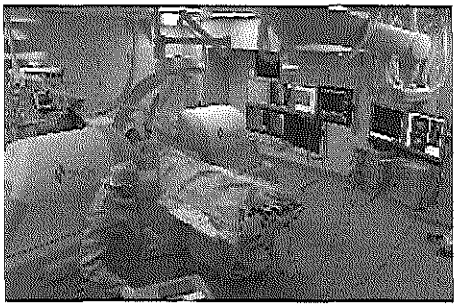


Figure 1. Magnetic navigation system is shown with the magnets in position on either side of the patient.

The magnetic navigation system has been described in detail previously[10,11]. Briefly, the interacting magnetic field produces a 15 cm uniform magnetic field of 0.08 Tesla that can be increased to 0.1 Tesla. Computer controlled movements of the magnets allow redirection of this externally applied magnetic field vector in 360° in all planes. For cardiac chambers a 3-D volume rendered reconstruction is imported and aligned for navigation. For coronary artery use, the 2-D locations of points on X-ray images are known in relation to the image intensifier, angiography system and table and this allows production of a 3-D reconstruction from 2 views separated by at least 30°. The result is real-time, on-table localisation of the reconstruction within the chest of a patient during a procedure to allow direction of therapy. Adjustment of the magnetic vectors from the model synchronised to the X-ray system adjusts tip-magnet direction in the patient to produce deflection of the wire. This gives reproducibly precise steering of the tip of the intravascular device and this steering is independent of the factors that can restrict conventional procedures such as poor transmission of manipulation.

New technology for progenitor/stem cell delivery

Previous methods for endocardial stem cell delivery had several drawbacks in identification, cell delivery and therapy. Identification of the sites for injections was poor and depended on strategies such as marking acetate sheets overlaid on the X-ray screen, delivery was time-consuming with poor targeting, and follow-up was hampered by imprecise knowledge of where the injections had been and therefore depended on generalised LV measurements rather then the region of interest.

The magnetic navigation system can integrate other 3-D volume rendered information such as MSCT, MRI or the NOGA® XP mapping system, see Figure 2, to give precise steering/direction of injections.

Infarct localisation is possible by current techniques such as MSCT, which is capable of identifying infarcted areas of myocardium[12], and integration can provide a 3-D volume rendered map of the damaged myocardium. However this information is not real-time and was of limited use in treating the patient on the table.

New technology is under current development. The NOGA® XP mapping system gives information on the functional and electrical properties of the myocardium simultaneously with real-time, precise localisation by producing a map of the left ventricle (see Figure 2). This may allow differentiation between the extent of the infarct and peri-infarct regions as well as giving valuable information for follow-up. This, together with the MyoStar™ injection catheter to allow magnetically enabled cell delivery (see Figure 3) may not only allow areas to be identified by electrical and mechanical mapping measurements but also deliver injections of cell therapy.

Potentially, this could give several major advantages. Firstly, integration of real-time electromechanical mapping would give a real-time, on-table 3-D LV map for exact localisation. Secondly, electromechanical mapping may discriminate between viable and non-viable infarcted areas e.g. identifying electrically active but non-contractile areas such as stunned myocardium. Therefore this combination of detection methods could enable new strate-

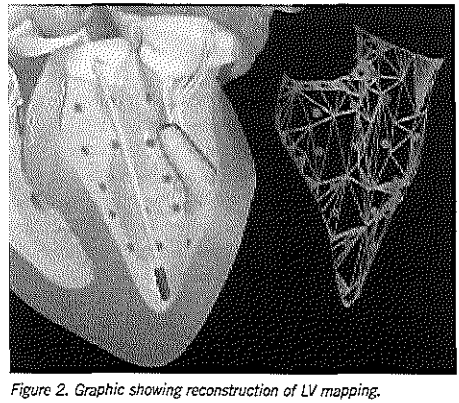


Figure 2. Graphic showing reconstruction of LV mapping.

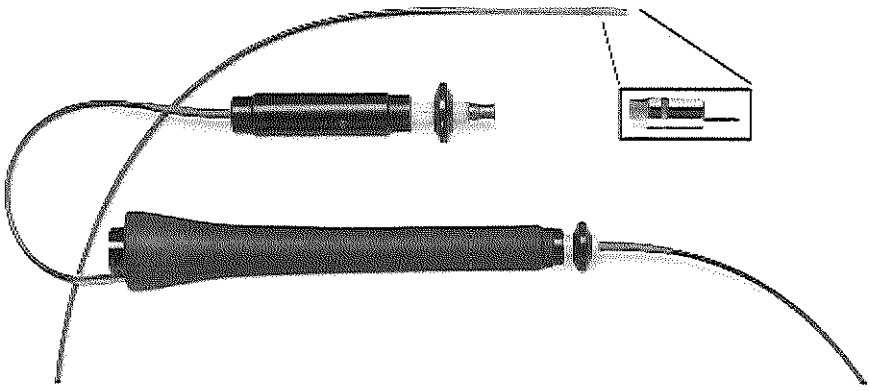


Figure 3. MYOSTAR™ injection catheter to have electromechanical guidance provided by the NOGA® XP.

gies that tailor delivery of cell therapy to particular areas. Thirdly, a magnetically navigable injection catheter could precisely direct cell injection and simultaneously integrate spatial and electrical information. Fourthly, an electromechanical map could aid follow-up both to identify the region on the map that was previously treated, and also to give quantifiable information for specific locations on the map. Definable delivery of stem cells would allow investigation of specific locations or patterns of cell delivery. As different parts of an infarcted area may have discordant electrical and mechanical properties, with intact electrical but poor mechanical activity, this may allow identification of stunned myocardium in penumbral regions that might derive particular benefit from stem cell injection. Additionally, current estimates of the resolution of the new system suggest that this could localise positions to within 1 mm that would represent a major improvement. An idea of the type of the information that may be available with this system for diagnosis and follow-up is seen in Figure 4.

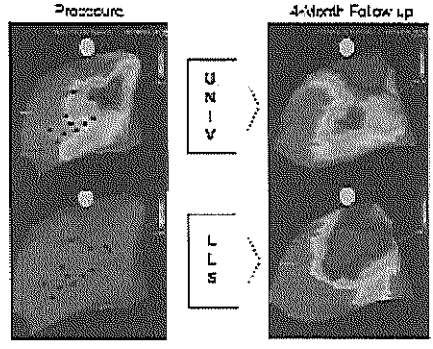


Figure 4. NOGA™ electrical (UNIV, at top) and mechanical (LLS, at bottom) maps from a human patient in the stem cell treatment group. The maps on the left are those performed at the time of injection and maps at right are those at four month follow-up. An area of viability, showing normal electrical activity, can be noted on the upper right map. The maps on the right show improvement in both electrical and mechanical function. LLS = linear local shortening; UNIV = unipolar voltage.

Limitations of current cell delivery techniques

The strategy of endocardial injection has suffered from a number of limitations. The current technique of LV angiography gives mediocre localisation as the entire LV volume is seen only in 2-D pictures from different views. This technique gives little idea of the location of the watershed or penumbral area that might contain stunned rather then necrotic cells. Injection sites, and particularly areas that might be particularly susceptible to improvement with cell therapy, are poorly identifiable in real-time, and are difficult to access with current equipment.

Intracoronary injection has been the other widely used technique and has its own limitations. Release of cells depends on haematogenous spread, and this may be poor in areas that are poorly revascularised or are still occluded, therefore reducing the effectiveness in these areas. This inhomogeneous delivery may prevent delivery to salvageable areas that have competitive flow from a neighbouring territory that is, however, insufficient for long-term survival. As intracoronary injection often uses occlusion of the proximal vessel this results in further ischaemic insult with further, possibly irreversible, damage and cell loss and reduced perfusion pressure leading to collapse of pinched microvasculature. Additionally, loss of cells that do pass through the microvasculature into the general circulation, also known as 'shedding', may lead to the drawback of these progenitor cells reaching areas where conditions favourable for angiogenesis are present but clinically unwanted, e.g. neoplastic neovascularisation or ischaemic areas such as retinopathy.

Implications for the clinical situation of cell delivery

Two particular situations may be particularly appropriate for treatment of cell therapy; these are recent anterior infarction with significant LV impairment and non-revascularisable chronic ischaemic cardiomyopathy. While these situations have some similarity such as extensive cell loss and unattractiveness for cardiothoracic surgery, there are specific reasons why precisely directed endocardial injection may hold particular advantages. These have advantages over and above the general advantages of improved diagnosis with two modalities, precise site-directed delivery and follow-up discussed above.

The purpose of using cell therapy in the treatment of recent acute MI is to prevent maladaptation or remodelling and so preserve LV contractile function and thus exercise tolerance. This group may be the most effective group to treat with cell therapy in order to maximise myocardial cell salvage. As discussed above, endocardial injection may be advantageous over intracoronary delivery as it delivers cells to areas that have a restricted or absent blood supply. This direct delivery via the endocardium overcomes the problem of tissue swelling related to ischaemic damage that may cause pinching of the microvasculature to reduce haematogenous delivery to peripheral sections of the infarct territory, i.e. to the penumbral areas that may be particularly suitable for salvage. In addition, endocardial injection decreases shedding of cells into the circulation since cells are injected within the tissue thus placing decreased numbers of cells into the bloodstream.

In the treatment of chronic heart failure there has already been tissue loss and often, this is combined with severe ischaemic coronary disease. Cell therapy aims to reverse the chronic changes by improving the vascular bed and salvaging as much myocardium as possible. This situation would particularly benefit from addition of new myocardial cells, although the ability to produce new myocytes remains controversial. Precise delivery to electrically and mechanically definable areas could allow uniform coverage or other distributions to target specific areas. In addition the risk of perforation of a thin myocardium may be minimised by use of electrical signals via the adjustable and retractable needle providing exact depth control together with monitoring of the ECG for reverse potentials.

Revascularisation

A further option enabled by the magnetic navigation system is the ability to treat complex coronary disease. As the predominant cause of LV dysfunction is ischaemic heart disease, the partial or complete recovery of the native coronary circulation may encourage both recovery of native myocytes and provide a milieu for better uptake and differentiation of stem cells.

The ability of the system to support PCI has been demonstrated in a number of scenarios from simple to complex lesions[13] and evidence suggests that this system may be particularly advantageous in more difficult anatomy[14] and is capable of successfully treating CTOs[15]. The integration of MSCT data (see Figure 5) allows the missing segment of the vessel to be judged (see Figure 6) and the superimposition of this data by co-registration gives an indication of the pathway.

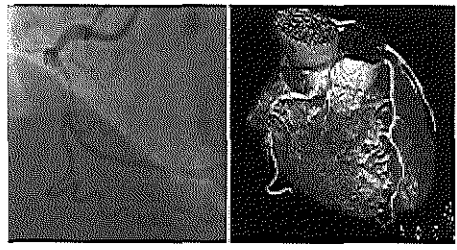


Figure 5. The panel on the left shows the raw data from angiography and the panel on the right shows the reconstructed MSCT.

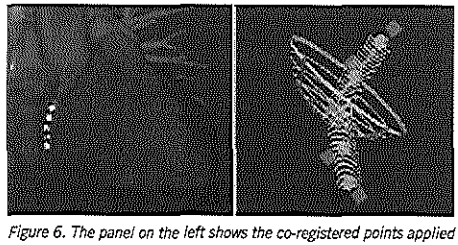


Figure 6. The panel on the left shows the co-registered points applied to the MSCT image that was imported into Navigant and the panel on the right shows the computer reconstructed pathway that is derived from CT and projected onto the reconstruction in Navigant.

Conclusion

Magnetic navigation may aid the performance of cardiac stem cell transplantation by allowing integration of spatially localised, 3-D volume rendered information with real-time tissue visualisation in multiple modalities to give site directed deliverability to reduce procedure times and irradiation, and improve efficacy simultaneously. The development of the NOGA® XP system and the magnetically navigable MyoStar™ injection catheter may lead to improved detection of non-functional myocardium, better delivery and more precise follow-up.

Acknowledgement

The authors are grateful to Joep Maeijer for his help in the preparation of the images.

References

1. World Health Organization (WHO). The atlas of heart disease and stroke. Geneva: World Health Organization; 2004.

2. Pfeffer, J.M., Pfeffer, M.A., Fletcher, P.J. & Braunwald, E. Progressive ventricular remodeling in rat with myocardial infarction. *Am. J. Physiol.* 1991;260:H1406-1414.

3. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation.* 1987;76:44-51.

4. Kocher AA, Schuster MD, Szabolcs MJ, Takuma S, Burkhoff D, Wang J, Homma S, Edwards NM, Itescu S. Neovascularization of

ischemic myocardium by human bone-marrow- derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function. *Nat Med.* 2001;7:430-436.

5. Tse HF, Kwong YL, Chan JK, Lo G, Ho CL, Lau CP. Angiogenesis in ischaemic myocardium by intramyocardial autologous bone marrow mononuclear cell implantation. *Lancet.* 2003;361:47-49.

6. Tomita S, Li RK, Weisel RD, Mickle DA, Kim EJ, Sakai T, Jia ZQ. Autologous transplantation of bone marrow cells improves damaged heart function. *Circulation.* 1999;100:247-256.

7. Makino S, Fukuda K, Miyoshi S, Konishi F, Kodama H, Pan J, Sano M, Takahashi T, Hori S, Abe H, Hata J, Umezawa A, Ogawa S. Cardiomyocytes can be generated from marrow stromal cells *in vitro*. *J. Clin. Invest.* 1999;103:697-705.

8. Assmus B, Schachinger V, Teupe C, Britten M, Lehmann R, Dobert N, Grunwald F, Aicher A, Urbich C, Martin H, Hoelzer D, Dimmeler S, Zeiher AM. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction. (TOPCARE-AMI). *Circulation.* 2002;106:3009-3017.

9. Meyer GP, Wollert KC, Lotz J, Steffens J, Lippolt P, Fichtner S, Hecker H, Schaefer A, Arseniev L, Hertenstein B, Ganser A, Drexler H. Intracoronary bone marrow cell transfer after myocardial infarction: eighteen months' follow-up data from the randomized, controlled BOOST (BOne marrOw transfer to enhance ST-elevation infarct regeneration) trial. *Circulation.* 2006;113:10:1272-4.

10. Tsuchida K, Garcia-Garcia HM, van der Giessen WJ, McFadden EP, van der Ent M, Sianos G, Meulenbrug H, Ong AT, Serruys PW. Guidewire navigation in coronary artery stenoses using a novel magnetic navigation system: first clinical experience. *Catheter Cardiovasc Interv.* 2006;Mar;67(3):356-63.

11. Patterson MS, Schotten J, van Mieghem C, Kiemeneij F, Serruys PW. Magnetic Navigation in Percutaneous Coronary Intervention. *Journal of Interventional Cardiology.* 2006;19:558-565.

12. Nieman K, Cury RC, Fecencik M, Nomura CH, Abbara S, Hoffman U, Gold HK. Jang I-K, Brady TJ. Differentiation of recent and chronic myocardial infarction by cardiac computed tomography. AJC 2006; doi:10.1016/j.amjcard.2006.01.101.

13. Patterson MS, van Geuns RJ, Tanimoto S, Tsuchida K, Serruys PW. Magnetic Navigation with the Endo-Luminal View and the X-ray overlay - Major advances in novel technology. *Accepted for publication in Eurointervention.*

14. Ramcharitar S, Patterson MS, Serruys PW. Randomised controlled study comparing conventional wires with magnetic guided wires in a tortuous phantom. *Catheter Cardiovasc Interv.* 2006 Dec 26; [Epub ahead of print].

15. García-García HM, Tsuchida K, van Mieghem C, Daemen J, van Weenen S, Patterson M, van der Ent M, van der Giessen WJ, Meulenbrug H, Sehra R, de Feyter P, Serruys PW. Multi-Slice Computed Tomography and Magnetic Navigation - Initial experience of cutting edge new technology in the treatment of Chronic Total Occlusions. *Accepted for publication in Eurointervention.*

PART 6

DEVELOPMENT OF NEW DRUGS FOR THE TREATMENT OF PATIENTS WITH ACUTE CORONARY SYNDROMES UNDERGOING PERCUTANEOUS CORONARY INTERVENTIONS

CHAPTER 26

HAEMODYNAMIC EFFECTS, SAFETY, AND TOLERABILITY OF HAEMOGLOBIN-BASED OXYGEN CARRIER-201 IN PATIENTS UNDERGOING PCI FOR CAD

Clinical research

EuroIntervention

Haemodynamic effects, safety, and tolerability of haemoglobin-based oxygen carrier-201 in patients undergoing PCI for CAD

Patrick W Serruys[1]*, MD, PhD; Pascal Vranckx[2]*, MD; Ton Slagboom[3], MD; Evelyn Regar[1], MD; Emanuele Meliga[1], MD; Robbert J de Winter[4], MD, PhD; Guy Heyndrickx[5], MD, PhD; Gerhard Schuler[6], MD, PhD; Eric AM van Remortel[7]; Gregory P Dubé[8], PhD; Janette Symons[9], for the COR-0001 trial investigators

1. Department of Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands; 2. Department of Cardiac Intensive Care & Interventional Cardiology, Virga Jesse ziekenhuis, Hasselt, Belgium; 3. Department of Interventional Cardiology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands; 4. Department of Cardiology, AMC, Amsterdam, The Netherlands; 5. Department of Cardiology, Onze Lieve Vrouwe ziekenhuis, Aalst, Belgium; 6. Department of Cardiology, Heartcenter, University Leipzig, Leipzig, Germany; 7. Statistician, Cardialysis B.V., Rotterdam, The Netherlands; 8. Biopure Corporation, Cambridge, MA, USA; 9. Clinical Trial Manager, Cardialysis B.V., Rotterdam, The Netherlands

* *These two authors have equally contributed to the manuscript.*

Under the Guest Editorship: Cindy Grines, MD, Division of Cardiology, William Beaumont Hospital, Royal Oak, Michigan, USA

Financial Disclosure: The investigators have no conflict of interest related to the sponsor of this study or the study medication.
Funding/Support: This work was supported by a grant from The Biopure Corporation, Cambridge, MA, USA

This paper also includes accompanying moving images published at the following website: www.eurointervention.org

KEYWORDS
Coronary intervention, acute coronary syndromes, haemoglobin-based oxygen carrier

Abstract

Aims: Haemoglobin based oxygen carriers (HBOCs) are considered in the treatment of patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI). In light of their potential vasopressor and colloidal properties, their effect on coronary physiology, safety and tolerability needs to be established.

Methods and results: In this phase II pilot trial, 45 patients were randomly assigned, (1:1:1) to double blind treatment with a 30 minute intravenous (IV) infusion of either 15 or 30 g of HBOC-201, compared to an equivalent volume of non-oxygen carrier colloid control. Systemic, pulmonary, and coronary haemodynamics were studied during this infusion period. IV HBOC-201 administration produced an increase in systolic blood pressure (SBP), pulmonary capillary wedge pressure and calculated systemic vascular resistance (SVR) and a concomitant decrease in cardiac output (CO); there was a decrease in mixed venous saturation (SVO2) following IV HBOC-201. The left ventricular stroke work index (LVSWI) was not altered by HBOC-201 treatment. Of note, no coronary vasoconstriction was observed, nor were there significant changes in resting average peak velocity (APV), coronary-artery diameter, volumetric coronary blood flow, or coronary vascular resistance. The percentage of patients with adverse events did not differ between the HBOC-201 treated and control groups (76% vs. 63%, respectively, P=0.49). Seven serious adverse events (SAE) occurred in six patients in the treatment group and two in two patients in the control group. Only one SAE (hypertension) was judged HBOC-201 related. Patients in both the HBOC-201 and control group had a similar incidence of increased liver alanine transaminase (31% vs 31%, respectively, NS); 10% of the patients in the HBOC-201 group had increases greater than three times the upper limit of normal. Differential increases were noticed in some inflammatory markers (IL-6, CRP) 18-24 hours after infusion between the HBOC-201 arms and the control group.

Conclusion: No compromise in the coronary blood flow or LVSWI was observed despite HBOC-201's known vasoactive effects. One SAE was adjudicated as "drug related" and fully resolved. The clinical relevance of the differential rise in certain biochemical markers and the adverse effects of plasma haemoglobin in the context of ACS needs further investigation.

* *Corresponding author: Thoraxcenter, Ba583a, Erasmus Medical Centre, 's Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands*
E-mail: p.w.j.c.serruys@erasmusmc.nl

Introduction

Prompt reperfusion of ischaemic myocardium is the major focus of acute treatment of patients with ST-segment elevation myocardial infarction (STEMI). With (primary) PCI emerging as the new gold standard of ACS reperfusion therapy, new questions are arising about the best pharmaco-invasive strategy to limit the amount of myocardial damage occurring during the ischaemia and early reperfusion periods. Because of their ability to deliver oxygen, HBOCs have been considered for use in the treatment of ACS.

HBOC-201 is a cell-free polymerised bovine-haemoglobin solution in a balanced salt solution. HBOC-201 may act as a direct tissue oxygen donor and an "oxygen bridge" between RBCs and tissues[1,2], facilitating oxygen transport from erythrocytes through plasma to the endothelium and organs and eventually to post-stenotic areas where plasma oxygen transport can improve tissue oxygenation.[3] HBOC-201 can be stored at room temperature for a period of up to three years. In a dog myocardial ischaemia-reperfusion model, infusion of HBOC-201 prior to coronary artery occlusion reduced myocardial infarct size.[4,5] The current study is the first attempt at introducing HBOC-201 in the treatment of ACS and addresses safety issues in the controlled setting of elective PCI.

Methods

Study design

The COR-0001 trial was a randomised 3-arm (1:1:1), double-blind, placebo-controlled, dose-finding pilot (phase II) study designed to investigate the safety and tolerability of IV HBOC-201 versus an equivalent amount of artificial colloid in patients with stable angina and non-ST-segment elevation (NSTE) ACS scheduled for elective PCI.

The study had one control arm and two active treatment arms with HBOC-201 delivered at different doses. In one arm 230 ml HBOC-201, equivalent to 30 g bovine Hemoglobin (Hb) was infused over 30 minutes. In the second arm 115 ml of HBOC-201 was infused over 15 minutes, at the same infusion speed of the first arm; thus delivering 15 g of Hb, sequentially followed by a 115 ml infusion of Voluven-Fresenius (a colloidal volume expander chosen for its molecular weight, similar to that of the study drug). The control arm consisted of 230 ml Voluven-Fresenius infused over 30 minutes. Randomisation was stratified by clinical site, using permuted blocks of six patients.[6] Patients were allocated to a treatment by a central allocation telephone service. Patients, investigators and the members of the Data Safety Monitoring Board (DSMB) were blinded to the treatment allocation during the study period. For blinding purposes in the catheterisation laboratory a double dummy technique was used (see online-only Data Supplement for details). The study was performed under Medical Ethics Committee approval and in accordance with the Declaration of Helsinki.

Patient population

The patients were enrolled in five centres in The Netherlands, Germany and Belgium selected for their expertise in cardiac physiology studies (Appendix 1, online-only Data Supplement).

Patients were eligible for the study if they had either unstable angina or NSTE ACS and had a severe stenosis in at least one coronary artery eligible for PCI. All patients had to provide written informed consent. Major exclusion criteria were: significant haemodynamic compromise requiring inotropic or vasopressor support, significantly altered left ventricular function (ejection fraction <35%), severe hypertension (>180/110 mmHg) not adequately controlled by antihypertensive therapy at time of study entry, renal impairment (serum creatinine >1.6 mg/dl) or contra-indications to the use of adenosine and/or standard drugs for coronary intervention and coronary artery disease. The patient weight at inclusion was limited to a maximum of 110 kg.

Study procedures

The catheterisation laboratory procedure was divided into three consecutive phases: the baseline, the study drug infusion period (230 ml solution/30 minutes) and the index PCI procedure. Haemodynamic monitoring and control angiography were performed at baseline and at three consecutive time points (10', 20', 30') during the study drug infusion period. PCI, including adjunctive therapies, were performed according to standard institutional practices. No standard medications used in the management of patients with ischaemic heart disease were withheld by the study protocol, stopping rules on study drug infusion were predefined (online-only Data Supplement).

Safety endpoints and assessments

The primary endpoint of the study was the in-hospital safety assessment including systemic and coronary haemodynamics, thrombotic events, untoward drug interaction effects, allergic reactions, drug-dye interactions, met-haemoglobin formation, serious adverse events, as well as biochemical markers of inflammation, myocardial necrosis, renal and hepatic function. The extent of deviation of blood values beyond the limits of normal was graded by the DSMB/CEC members. Calculated measurements of eGFR (estimated glomerular filtration rate) by the Cockroft-Gault equation were used for estimating and reporting renal dysfunction.[7] Additional analysis included a 30-day clinical follow-up, death (all-cause mortality), recurrent myocardial infarction, recurrent myocardial ischaemia and serious adverse events.

Patient symptoms and adverse events were evaluated by the study investigators using a graded severity index.[8] An independent Data Safety Monitoring Board/ Clinical Event Committee (DSMB/CEC) reviewed aggregate safety data (including blood values) to identify potential patient safety issues. Safety monitoring and adjudication of clinical events with respect to their clinical relevance was performed by this committee. The data as classified by the DSMB/CEC was used in the final safety analysis unless otherwise specified.

A doppler steerable guidewire (0.36 mm [0.014 in.] in diameter) (Flowire, Volcano Corporation, Rancho Cordova, CA, USA) was positioned in a reference coronary artery without any significant stenosis and was coupled to a real-time spectrum analyser and video cassette recorder. Coronary flow velocity and coronary flow reserve measurements were performed at baseline and after the study drug infusion period in the first 30 consecutive study patients.

To assess coronary flow reserve (the ratio of peak hyperaemic velocity to average peak velocity at base line), maximal hyperaemia was induced with peripheral IV infusion of adenosine (140 µg/kg/min).[9] Each measurement was duplicated to check for consistency. Coronary blood flow was calculated as follows: (the average peak velocity ÷ 2) x the cross-sectional area of the coronary artery, calculated as πr^2 (diameter of the artery ÷ 2)^2, which assumed a time-averaged parabolic velocity profile and a cylindrical coronary artery.[10] Coronary vascular resistance (in mmHg/ml/min) was calculated for the reference vessels as the mean arterial pressure divided by the coronary blood flow. The coronary vascular resistance index was calculated as the average peak velocity (APV) hyperaemic divided by the mean arterial pressure at rest.

Quantitative coronary angiographic assessments of the vessel segment comprising the flow wire as well as the coronary diameter at the tip of the Doppler wire, (between two side branches), were performed by an independent core laboratory (Cardialysis, Rotterdam, The Netherlands) with the use of edge-detection techniques.[11]

Systemic haemodynamic measurements included arterial blood pressure, recorded from a 7 Fr guiding catheter in the ascending aorta; pulmonary-artery and capillary wedge pressure (measured from the distal port of a 7 Fr Swan-Ganz catheter) and right atrial pressure (measured from the proximal port of the Swan-Ganz catheter). The heart rate and cardiac output, determined by thermodilution, were also recorded. Standard haemodynamic formulas were used to calculate systemic and pulmonary vascular resistance and their indexes.

Statistical analysis

Continuous baseline characteristics were analysed with one way analysis of variance and categorical variables with the Fisher's Exact test. For individual variables, values during and after administration of the study drug were compared with base-line values by a mixed model analysis of variance on change from pre-infusion with the factors of time, treatment and time by treatment interaction. The different groups were compared by an analysis of covariance with treatment as a factor and the pre-infusion value as a covariate. Multiple comparisons between the treatment groups were performed with the Bonferroni correction. Differences were considered significant when P values were less than 0.05. All statistical analyses were performed with SAS version 8.

Cardialysis (Rotterdam, The Netherlands) was the core laboratory for angiographic and ECG analysis and the data management and coordinating centre. All listed authors (see appendix 1, online-only Data Supplement) participated in the study design, enrolment of patients, and/or data interpretation.

Results

Study population

A total of 47 patients were enrolled between December 2003 and March 2005. During this period, in November 2004, the Steering Committee temporarily suspended patient enrolment on the recommendation of the DSMB to permit a detailed analysis of a SAE described below. This SAE was adjudicated by the committee and individual review to be procedure and not drug related. The study was allowed to resume in January 2005. At this occasion the DSMB raised it's concern about the critical elevations in SBP following IV HBOC-201 encountered in some patients and a protocol amendment instructing SBP management was issued. Of the 47 patients randomised, one patient withdrew consent before any study drug infusion and one patient did not receive any study medication; both patients were excluded from analysis. The remaining 45 patients concluded the planned 30-day follow-up. Analysis was by intention to treat, including one patient in whom the 30 g dose was inadvertently infused instead of the 15 g dose.

As shown in Table 1, treatment groups were equally matched with respect to age, weight, anginal status and the overall cardiovascular risk profile at screening. There were five diabetic patients in the HBOC-201 group and none in the control group.

Table 1. Baseline characteristics of the study population.

	Control (n=16)	15 g HBOC-201 (n=17)	30 g HBOC-201 (n=12)
Age, years	60.6 ±7.5	56.8 ±10.3	62.8±6.5
Male	11 (69)	12 (71)	10 (83)
Weight	80.2±12.4	84.1±12.4	81.3±13.4
Stable angina	3 (19)	4 (24)	6 (50)
Unstable angina			
Total	13 (81)	13 (76)	6 (50)
Class IB	3 (19)	3 (18)	0
Class IIB	8 (50)	8 (47)	6 (50)
Class IIIB	2 (13)	2 (12)	0
Previous non-Q-wave MI	3 (19)	0	2 (17)
Previous PCI	3 (19)	1 (6)	2 (17)
Diabetes Melitus	0	3 (18)	2 (17)
Hypercholesterolaemia	6 (38)	4 (24)	9 (75)
Cigarette smoker	4 (25)	4 (24)	0
Hypertension	10 (63)	9 (53)	8 (67)
Diastolic blood pressure (mmHg)	75.3±13.4	77.6±11.2	72.3±12.2
Systolic blood pressure (mmHg)	131.0±20.5	141.7 ±18.4	139±18.0

Data is represented as numbers with percentages or as mean values with standard deviations.

Systemic hemodynamic effects

The most important haemodynamic effects of an IV infusion of HBOC-201 are summarised in Table 2. In both active treatment groups, there were significant increases in systemic arterial blood pressure (systolic, diastolic, or mean pressure) in conjunction with a significant reduction in cardiac index at 30 minutes after HBOC-201 infusion. The calculated systemic vascular resistance (SVR) (and pulmonary vascular resistance, PVR) was significantly increased in these patients. A dose relationship could not be established for these phenomena (Figure 1a-b-c-d). Critical elevations in SBP following IV HBOC-201 administration, for the purpose of this study defined as a SBP >180 mmHg, was seen in

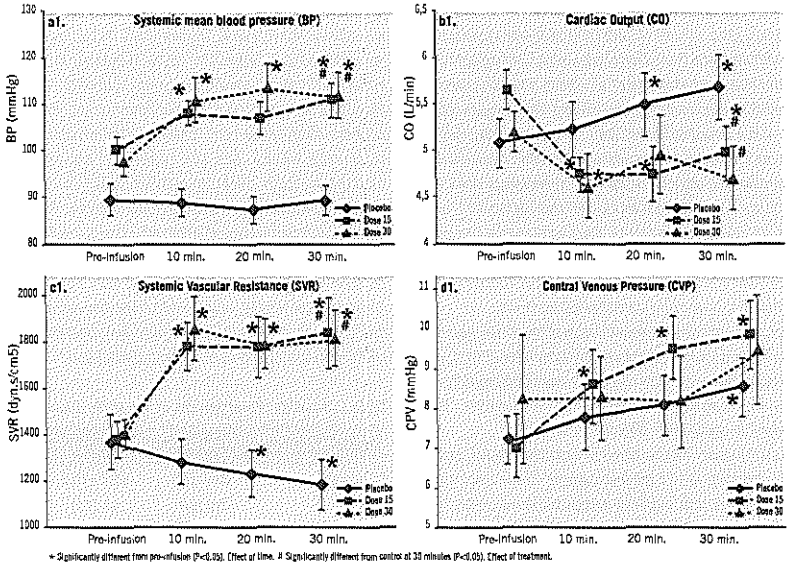


Figure 1.1 Relative change with respect to baseline values in systemic mean blood pressure (a), cardiac output (b), systemic vascular resistance (c) and central venous (right atrial) pressure (d). Effect of control or IV HBOC 15 g and 30 g on MBP (a1), SVR (b1), CO (c1) and CVD (d1).

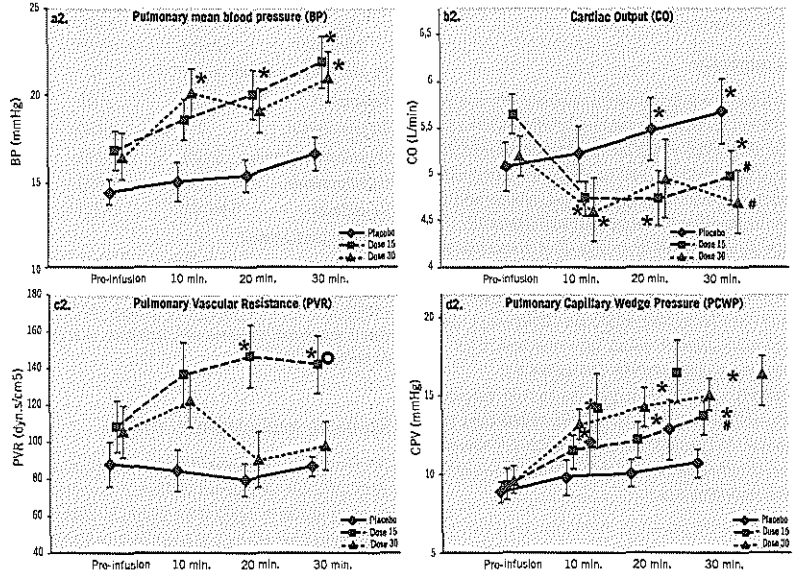


Figure 1.2 Relative change with respect to baseline values in pulmonary mean blood pressure (a), cardiac output (b), systemic vascular resistance (c) and pulmonary cardiac wedge pressure (d). Effect of control or IV HBOC 15 g and 30 g on PAP mean (1.2a), PVR (1.2b), CO (1.2c) and PCWP (1.2d). Measurements were made at baseline (pre-infusion) and at three different time-points during a 30 minute infusion period: 10', 20' and 30'=end of infusion. Values are shown as means ±SD for all patients.

9/29 (31%) of the patients. Critical blood pressure elevations were reduced following the protocol amendment that instructed the use of appropriate antihypertensive treatment (IV nitroglycerin) when necessary; 7/20 (35%) patients before the amendment versus 2/9 (22%) patients post amendment. One patient was unresponsive to IV nitroglycerin and required nifedipine in order to control blood pressure. However, despite the reduction in absolute number of patients experiencing a clinically significant hypertensive episode, there was no difference between the amounts of nitroglycerin (NTG) used before and after the DSMB amendment instructing the use of NO donors to correct systolic blood pressure (a detailed description is provided in the online-only data supplement). At two hours post infusion (data not shown), any statistical difference in MAP remained between the active treatment groups and the control group. A significant decrease in heart rate was seen only in the HBOC-201 15 g group.

In all three groups the pulmonary capillary wedge pressure (PCWP) increased following infusion at 30 minutes; the increment was significantly greater in both HBOC-201 groups compared to control, (Table 2, Figure 1.2-d), never reaching the predefined critical level of 20 mmHg. There were no significant changes in calculated left ventricular stroke work index.

A significant decrease in mixed venous saturation (SVO2) was noticed following IV HBOC-201 (baseline: 77.4%±7.7%, 30 minutes: 70.7%±8.3%, p=0.002); in seven patients below the level of 65 %. However, the index of systemic oxygen consumption (VO2), assuming an arterial oxygen saturation (SaO_2) of 97% in all patients, did not change from baseline (calculation, see online-only data supplement).

Coronary haemodynamic effects

The effects of IV HBOC-201 on the diameter of coronary arteries (reference vessel) and on flow velocity before and after IV adenosine administration are shown in Table 3. Intravenous administration of HBOC-201 caused no significant changes in the resting APV, coronary-artery diameter or coronary vascular resistance. The coronary blood flow velocity reserve tended to increase and this

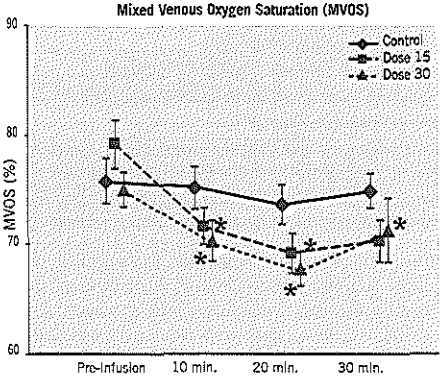


Figure 2. Relative change SVO2 with respect to baseline values. Measurements were made at baseline (pre-infusion) and at three different time-points during a 30 minute infusion period: 10', 20' and 30'=end of infusion. Values are shown as means±standard error.

Table 2. Systemic and pulmonary haemodynamic variables at baseline and at the end of the study drug infusion period.

	15 g HBOC-201 (n=17)			30 g HBOC-201 (n=11)			Control (n=16)		
Variable	Baseline	Post Infusion	P value (+)	Baseline	Post Infusion	P value (+)	Baseline	Post Infusion	P value (+)
Systolic Blood Pressure (mmHg)	145±24	153±30*	0.34	140±15	158±26*	0.006	126±25	123±20	0.49
Mean Arterial Pressure (mmHg)	100±12	111±15*	0.02	97±11	112±16*	<0.001	90±13	90±13	0.95
Pulmonary Arterial Pressure (mmHg)									
Systole	24±7	29±7	0.002	23±7	30±8	0.003	21±5	24±5	0.13
Diastole	12±5	16±7	0.006	12±5	15±4	<0.001	11±3	12±4	0.30
Mean	17±5	22±6	0.001	17±5	21±5	<0.001	14±3	17±4	0.06
Pulmonary-capillary wedge pressure (mmHg)	9±4	14±4*	<0.001	10±3	15±3	<0.001	9±3	11±3	0.09
Heart rate (beats/min)	69±8**	60±8	0.001	57±9	57±12	0.46	60±8	59±7	0.36
Cardiac index (litres/min/m^2)	2.87±0.49	2.51±0.56*	0.008	2.66±0.36	2.45±0.55*	0.16	2.64±0.44	2.94±0.59	0.002
Systemic-vascular resistance index (dyn.sec.cm-5)	1339±270	1820±527*	<0.001	1409±236	1799±370*	<0.001	1289±369	1177±395	0.02
Left Ventricular Stroke Work Index (g.m/m^2)	51±11	54±11	0.52	55±5	59±20	0.29	49±11	57±13	0.07

Data is represented as numbers and percentages or mean values with standard deviations

n: Number of patients per indicated group

(+): P values calculated with the mixed linear analysis of variance model

*: Different from control (P<0.05). Calculated with analysis of covariance with baseline value as covariate

**: Different from control and HBOC-201 30 g (P<0.05). Calculated with one-way analysis of variance

Average for baseline/post infusion is derived from matched data

In the high dose treatment group, data were available for 11 out of 12 patients

Table 3. Coronary haemodynamics at baseline and at the end of the study drug infusion period.

Variable	Baseline	Post infusion	P value (+)	Baseline	Post infusion	P value (+)
	HBOC-201 (n=20)			Control (n=11)		
Diastolic Systolic Velocity Ratio – at rest	1.78±1.03	1.50±0.65*	0.03	1.62±0.40	1.91±0.87	0.19
Average Peak Velocity – hyperemic (cm/sec)	45±18	57±25*	0.01	36±16	34±14	0.59
Average Peak Velocity – at rest (cm/sec)	18±8	22±12	0.09	19±8	18±4	0.60
Coronary Flow Reserve	2.64±0.93	2.70±0.72	0.74	2.10±0.98	1.97±0.81	0.67
	HBOC-201 (n=15)			Control (n=10)		
Mean Arterial Pressure – at rest (mmHg)	97±10	116±14	<0.001	102±14	99±11	0.37
Coronary Blood Flow – at rest (mL/min)	28±13	33±20	0.26	28±13	25±15	0.72
Coronary Artery Diameter by QCA (mm)	2.72±0.68	2.63±0.77	0.35	2.53±0.50	2.35±0.49	0.43
Coronary Vascular Resistance – at rest (mmHg/ml/min)	4.32±2.28	4.78±2.82	0.68	4.52±2.30	5.00±2.60	0.64
	HBOC-201 (n=19)			Control (n=10)		
Coronary Vascular Resistance index	0.47±0.16	0.49±0.21	0.36	0.35±0.14	0.35±0.14	0.99

Data is represented as mean values with standard deviations followed by number of observations. *: Different from control at (P<0.05). Calculated with analysis of covariance with baseline value as covariate. (+) P value calculated with mixed linear analysis of variance model. Mean±SD followed by number of observations. Coronary Vascular Resistance: – At baseline 6 missing values (4 missing reference diameter, 2 missing Mean Arterial Pressure/Average Peak Velocity); – At post infusion 7 missing values (5 missing reference diameter, 2 missing Mean Arterial Pressure/Average Peak Velocity); For mean arterial pressure, coronary blood flow and coronary artery diameter, only patients with an existing value for coronary vascular resistance are included.

increase may be related to a significant augmentation in driving pressure. A detailed QCA analysis of the reference vessel did not show any angiographic coronary vasoconstriction brought about by the study drug (Table 1, online-only Data Supplement). Coronary flow studies were terminated early (n=31) after a futility analysis by the DSMB considering the presented data and the potential patient burden of this invasive procedure.

Safety and tolerability

This study was aimed at providing as much safety information as possible about the IV administration of HBOC-201 in acute cardiology and PCI. The mean [±SD] amount of study drug solution infused in this study was: 238.1 (±34.2) ml for the 15 g HBOC-201group, 230.3 (±3.0) ml for the 30 g HBOC-201 group and 247.9 (±67.2) ml for the Voluven only group. One patient accidentally received two units of Voluven. In none of the patients did the study drug infusion have to be stopped for pre-defined safety reasons.

Patients were followed up for 30 days post PCI. During this period, no additional SAE occurred. The number of patients who experienced at least one adverse event was higher in the active treatment groups (75.9% pooled), as compared to the control group (62.5%) (Table 4), the difference is not significant statistically (p-value=0.49). In total, eighteen adverse events were considered to be study drug related,

Table 4. Reported adverse events (serious and non-serious).

		Control (n=16) Ne,Np (%)	15 g HBOC-201 (n=17) Ne,Np (%)	30 g HBOC-201 (n=12) Ne,Np (%)	Pooled HBOC-201 (n=29) Ne,Np (%)
Adverse events	Total	15,10 (63)	19,11 (65)	23,11 (92)	42,22 (76)
	Product-related	0	6,6 (35)*	12,8 (67)*	18,14 (48)*
	Procedure-related	5,5 (31)	2,2 (12)	6,5 (42)	8,7 (24)
Serious adverse events	Total	2,2 (13)	3,2 (12)	4,4 (33)	7,6 (21)
	Product-related	0	1,1 (6)	0	1,1 (3)
	Procedure-related	0	1,1 (6)¶	1,1 (8)	2,2 (7)
Serious adverse events as coded by ICD-9 code	Abdominal pain	0	1,1 (6)	0	1,1 (3)
	Cardiac arrest	0	1,1 (6)¶	0	1,1 (3)¶
	Chest pain	1,1 (6)	0	0	0
	CVA	0	1,1 (6)¶	0	1,1 (3)¶
	GI haemorrhage (low)	0	1,1 (6)¶	0	1,1 (3)¶
	Haematemesis	0	0	1,1 (8)	1,1 (3)
	Hypertension[GDube1]	0	1,1 (6)	0	1,1 (3)
	Non-ST-segment elevation acute coronary syndrome	1,1 (6)	0	3,3 (25)	3,3 (10)
	Malaise & fatigue	0	0	1,1 (8)	1,1 (3)
	Nausea & vomiting	0	0	1,1 (8)	1,1 (3)

n: number of patients; Ne=number of events; Np=number of patients that experienced an event; %: percentage of patients that experienced the event; CVA: Cerebro Vascular Accident; GI: Gastro Intestinal; ¶: the same patient; *: different from control (P<0.05). Calculated with Fisher's Exact Test. Hypertension: table only includes hypertensive episodes reported by the investigators (table 4 bis: incidence of critical elevations of blood pressure adjudicated by CEC, online version only)

one of which (a hypertensive episode) was serious. The difference in the number of events between the IV HBOC-201 treatment groups and the Voluven groups was mainly driven by the rise in liver (n=6) and/or pancreas enzymes (n=1) and the number of hypertensive episodes (n=10) (SBP>180 mmHg). In addition, one HBOC-201-treated patient experienced abdominal pain.

One patient suffered a periprocedural electromechanical dissociation (EMD), which followed a prolonged wedging of the guiding catheter during the PCI procedure. The patient required a prolonged resuscitation in the catheterisation laboratory. The clinical evolution was complicated by a watershed cerebral infarction and lower gastrointestinal bleeding. The patient experienced a full recovery. This incident was subject to detailed investigation by the DSMB supported by an independent neurologist while patient enrolment in the study was temporarily suspended. The EMD, reported as an SAE, was adjudicated to the procedure and not to the study drug; the neurological event reported as an SAE was putatively attributed to the period of hypotension experienced during the prolonged cardiac resuscitation of this patient. The cardiac arrest and "watershed infarction" were counted as one event.

No clinically significant changes were noted in haematological or chemical values following IV HBOC-201, except for the cardiac markers and liver transaminases. A significant rise in CK-MB levels >3 times ULN was documented in one patient, but this enzyme abnormality was not likely due to HBOC-201 treatment as the patient suffered procedure related serious complications and had a prolonged resuscitation period.

Through hospital stay, patients in both the HBOC-201 and control group had a similar incidence of increased liver alanine transaminase (31% vs 31%, respectively, NS); 10% of the patients in the active HBOC-201 group had elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or lactate hydrogenase (LDH) enzymes (>3 times ULN) compared with none in the control group (Table 5). No patients had an abnormal total bilirubin (>3.0 mg/dl and ≥ 100% increase) or Alkaline Phosphatase (>250 IU/L and ≥ 100% increase) value, and no jaundice or hyper bilirubinaemia was reported. Two patients in the treatment group showed an increase in pancreatic enzymes (serum amylase >1.5 ULN). No effect of the drug was observed on the renal function (Table 5). Overall, there was a slight increase in plasma methaemoglobin level following IV HBOC-201 (average value pre-HBOC: 0.50% / 6-8 hours post-HBOC: 0.75%, P= 0.007 and post 18-24 hours 0.90%, P<0.001) with two patients above the cut-off level of 1.0% (data not shown).

The IV HBOC administration was associated with a statistically significant differential increase in inflammatory markers (IL-6, and CRP), measured at 18-24 hours after HBOC infusion, between the treatment arms and the control group, without any clear dose response relationship (Figure 3).

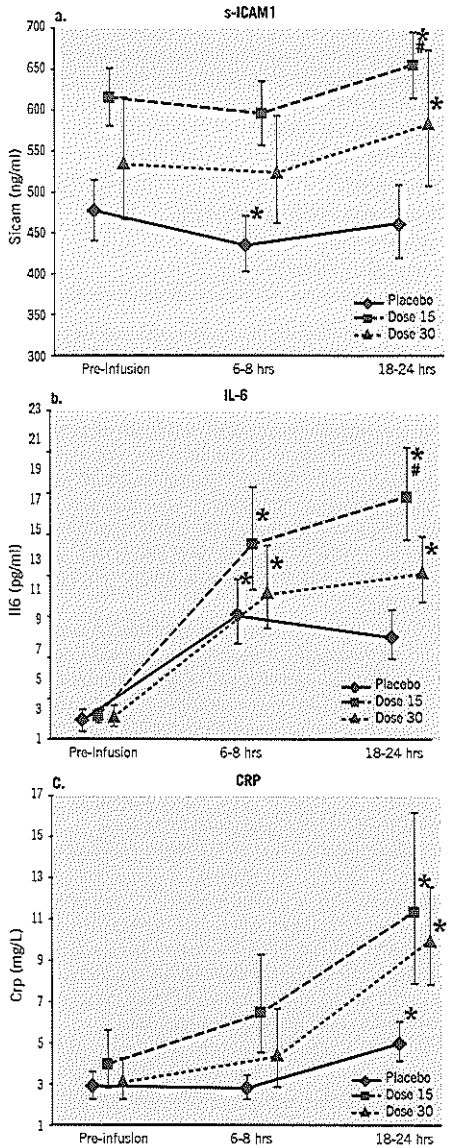


Figure 3. Effect of control or IV HBOC 15 g and 30 g on s-ICAM1 (a), IL-6 (b) and CRP (c). A dose relationship could not be established for any of these markers in the active IV HBOC-201 arms. Statistical analysis is performed on log-scale. For presentation, the geometric mean±the standard-error is given on the original scale.
** Significantly different from pre-infusion (P<0.05). Effect of time.*
 # Significantly different from control at 18-24 hours (P<0.05). Effect of treatment.

Discussion

We report on the first study in which HBOC-201 has been administered to patients with acute coronary syndromes undergoing PCI.

Table 5. Laboratory testing on organ function (liver/kidney)

	Control (n=16) N (%)	15 g HBOC-201 (n=17) N (%)	30 g HBOC-201 (n=12) N (%)
Peak AST > 3x ULN*	0	2 (13)	1 (8)
Peak ALT (SGPT) 1-3x ULN*#	5 (33)	4 (25)	2 (17)
Peak ALT (SGPT) > 3x ULN*	0	2 (13)	1 (8)
Peak ALP >2x ULN*	0	0	0
Increase in serum Creatinine (Cr) >0.5mg/dl	0	0	1 (8)
Decrease in eGFR>25% from baseline	1 (7)	0	3 (25)
↑Cr >0.5mg/dl or ↓eGFR>25%	1 (7)	0	3 (25)

*ULN: upper limit of normal: AST: aspartate aminotransferase; ALT: alanine transaminase; ALP: alkaline phosphatase; eGFR: estimated glomerular filtration rate.
Cut-off levels for total bilirubin, serum alanine aminotransferase and alkaline phosphatase levels were chosen according to the definition of drug-related hepatotoxicity.[25] The mean change in ALT expressed as a ratio (24 hrs follow up/Baseline) was 0.71 (control, P=0.02) vs 1.01 (HBOC-201, P=0.91), the mean change in ALP expressed as a ratio (24 hrs follow up/Baseline) was 1.07 (control, P=0.02) vs 1.11 (HBOC-201, P=0.09).
All 11 patients in this group had elevated ALT values at the baseline

Several haemoglobin-based oxygen carriers are currently being studied in clinical trials for various indications. Most are derived from human or bovine blood and have been chemically modified, resulting in molecules that differ in size, molecular weight, oxygen affinity, viscosity, and oncotic activity. Every formulation should be considered a unique drug with its own physical characteristics, pattern of biological activity, and profile of adverse reactions.

HBOC-201 is a cell free, endotoxin free, glutaraldehyde cross-linked bovine polyhaemoglobin in solution with an average molecular weight of 250 kDa (molecular weight ranging 130-500 kDa) and a viscosity less than plasma (1.3 centipoise at 37°C). Only trace amounts (2%) of unmodified haemoglobin and stabilised tetramer (molecular weight 65 kDa) are detected. HBOC-201 has an oxygen dissociation curve that is right-shifted with a P_{50} of 40 mmHg, compared to 27 mmHg for native human haemoglobin. These features provide excellent oxygen-transport properties.

The pathobiological effects of cell-free plasma haemoglobin are a concern.[12] Vascular homoeostasis is dependent on the compartmentalisation or physical separation of haemoglobin from the endothelium.[13] However, unlike single haemoglobin molecules, polymerised-HBOCs like HBOC-201, that are mostly in the form of large soluble haemoglobin complexes (98% is ≥ 130 kDa), are not expected to readily cross the intercellular endothelial junctions of blood vessels to exacerbate vasoconstrictive effects.

HBOC-201 is a colloid solution, and avoidance of circulatory overload is another important consideration. In our study population, a volume of up to 250 ml HBOC-201, equivalent to 30 g haemoglobin glutamer-250 bovine, was infused over a 30 minute time period. In none of the patients did the study drug infusion have to be discontinued for pre-defined safety reasons, such as an excessive increase in pulmonary wedge pressure.

IV HBOC-201 in this study population resulted in an increase in systolic blood pressure, a decrease in CO, and an increase in calculated SVR suggesting a vasoconstrictive effect. A critical elevation in SBP could be reversed by the intravenous administration of a nitric oxide donor, nitroglycerin, consistent with a putative role of nitric oxide scavenging in vasoregulation.[14-17]

The increase in SVR (afterload) in patients receiving HBOC-201 most likely contributed to the differential increase in PCWP between the control and treatment groups. The increase in preload observed after HBOC-201 must be interpreted as a normal physiological compensatory reaction to an increase in afterload (only observed in the HBOC-201 group) and to an increase in plasma volume expansion (induced in both groups). This increase in filling pressure does not reflect an intrinsic myocardial depressing effect of the compound nor a detrimental effect on the myocardial systolic function, since the Left Ventricular Stroke Work Index (LVSWI) remained unchanged regardless of the treatment received.

A decrease in mixed venous saturation was observed in both treatment arms and in some patients saturation went below 65% (Mean SVO_2 at baseline 77.4, at 30 minutes 70.7, p=0.002). The most plausible explanation for this phenomenon is a reduction in resting cardiac output associated with study drug infusion; consequently the arterio-venous O_2 difference would have to increase by lowering the mixed venous saturation. The metabolic demand of patients lying at rest on the cath lab table was probably unchanged and hence not a factor contributing to the fall in SvO2. There is no indication that IV HBOC-201 affected global oxygen consumption.

Our data clearly show that IV HBOC-201 had no effect on resting and hyperaemic coronary blood flow. This suggests that the autoregulatory mechanism of the coronary circulation was not adversely affected by the infusion of HBOC-201. In addition, there was no angiographic coronary vasoconstriction observed in the major epicardial vessel brought about by this drug.

This safety and feasibility study was designed to detect as many safety signals as possible; the DSMB was prospectively informed about the potential side effects of IV-haemoglobin solutions. The multitude of endpoints specifically scrutinised by either the investigators or the DSMB and CEC may have contributed to the apparently large number of adverse events reported.

Systemic removal of bioavailable nitric oxide has already been shown to contribute to clinical morbidities, including severe oesophageal spasm and dysphagia, abdominal pain and thrombosis.[17-19] The low incidence of these nitric oxide-related

clinical side effects in the present study, as compared to the literature, may be explained either by the lower dose of IV HBOC-201 used, by a concomitant use of nitric oxide donors and/or by the unique properties of the investigational drug.

A transient rise in concentrations of liver transaminases and/or pancreatic enzymes was seen in 10% of the patients following IV-HBOC-201. These patients were typically asymptomatic and without clinical sequelae during the 30 day follow-up. Since the liver is the normal Hb catabolic site, the absorption-distribution-metabolism and excretion (ADME) of HBOC-201 also involves the hepato-pancreatic systems, possibly inducing an upregulation of enzyme activity in response to an increased metabolic load. Elevations of transaminases and lipase have been observed in previous animal studies and clinical trials with HBOC-201. These enzyme elevations are generally not associated with hepatic or pancreatic dysfunction. The potential clinical importance of the increases in liver transaminases should be the subject of further investigation.

No adverse effect of the drug on renal function was observed. Nevertheless, given the recognised nitric oxide scavenging potential of the haemoglobin solutions, caution should be exercised when administering active HBOC-201 to patients with known renal dysfunction or in circumstances where the renal plasma flow is known to be reduced (i.e., NSAID use).

Nitric oxide reacts with oxyhaemoglobin to rapidly form the oxidation product, nitrate (NO_3^-), and methaemoglobin which is inactive.[20] The comparatively slow reduction of methaemoglobin back to the active form makes the formation of methaemoglobin of potential clinical importance. In this study, the plasma level of methaemoglobin increased slightly following IV HBOC-201, remaining within the physiological range in most of the patients. When the circulating methaemoglobin values in both treatment doses were pooled, a significant difference was found between the pre-infusion value versus the 18-24 hour value (ratio 1.76, p=0.003). This difference is not considered clinically significant.

In our study, the circulatory levels of hs-CRP, IL-6 and s-ICAM in the whole population remained in the broad range of variability observed in patients with ACS undergoing PCI.[21] The differential rise in circulatory levels of inflammatory markers following IV HBOC-201 compared to the control treatment is in accordance with previous observations indicating pro-inflammatory properties of plasma haemoglobin and heme.[22] Heme stimulates the expression of the adhesion molecules ICAM-1 (intracellular adhesion molecule-1), VCAM-1 (vascular cell adhesion molecule-1) and E-selectin on endothelial cells *in vitro*.[23,24] The clinical significance and extent of our observations has to be established in further work.

Study limitations: These results reasonably apply to medium- to low-risk patients suffering CAD and cannot be extrapolated to patients with an evolving or recent transmural myocardial necrosis or haemodynamic instability because such patients were excluded from this study. IV HBOC-201 might provoke more pronounced systemic haemodynamic effects in patients with other cardiovascular conditions or different baseline characteristics. The favourable profile of HBOC-201 in this trial warrants additional animal studies and clinical trials, including in particular, studies in higher risk ACS (STEMI) patient populations. The current trial did not focus on myocardial oxygen consumption or tissue oxygenation during IV HBOC-201. Investigation of HBOC-201 oxygen transport properties and the potential for this therapeutic to preserve myocardial tissue oxygenation in humans is currently under way.

In conclusion, despite its known vasopressor effect, intravenous administration of HBOC-201 does not interfere with the autoregulation of coronary blood flow both at rest and after maximal hyperaemia. The safety profile of HBOC-201 in this study reflects many of the known side effects of haemoglobin based solutions. When clinically contextualised, the SAEs observed in the HBOC-201-treated patients arose from other factors and, with the exception of increased blood pressure, were not considered product related. However, some adverse events (AEs) of cell-free plasma haemoglobin observed in this study remain a concern and need further investigation. This work provides a first step towards exploring a new pharmacological strategy that could broaden the temporal window for PCI, particularly in patients suffering a STEMI. While we recognise that this small population study did not include STEMI patients, investigated only two doses of HBOC-201 and was not aimed at demonstrating efficacy or beneficial effects of this oxygen carrier during ischemia, the results are encouraging enough to pursue additional studies to gather that information.

Acknowledgements

The authors would like to thank Ms. Samantha Young for her assistance with the preparation of the manuscript.

References

1. Page TC, Light WR, McKay CB, Hellums S. Oxygen transport by erythrocyte/hemoglobin solution mixtures in an in vitro capillary as a model of hemoglobin-based oxygen carrier performance. *Microvasc Res* 1998; 55: 54-64.

2. Page TC, Light WR, Hellums S. Prediction of microcirculatory oxygen transport by erythrocyte/hemoglobin solution mixtures. *Microvasc Res* 1998; 56: 113-126.

3. Standl T, Horn P, Wilhelm S, C Greim, M Freitag, U Freitag, A Sputtek, E Jacobs, and J Schulte am Esch. Bovine hemoglobin is more potent than autologous red blood cells in restoring muscular tissue oxygenation after profound isovolemic haemodilution in dogs. *Can J anaesth* 1996; 43 (7): 714-723.

4. Caswell JE, Strange MB, Rimmer DM, Gibson MF, Cole P, Lefer DJ. A novel hemoglobin-based blood substitute protects against myocardial reperfusion injury. *Am J Physiol Heart Circul Physiol.* 2005, 288: H1796-H1801.

5. George I, Yi GH, Schulman AR, Morrow BT, Cheng Y, Gu A, Zhang G, Oz MC, Burkhoff D, Wang J. A polymerized bovine hemoglobin oxygen carrier preserves regional myocardial function and reduces infarct size after acute myocardial ischemia. *Am J Physiol Heart Circ Physiol* 2006; 291: H1126-H1137

6. Matts JP, Lachin JM. Properties of permuted-block randomization in clinical trials. *Control Clin Trials.* 1988;9:327-344.

7. National Kidney Foundation. Clinical practice and guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kid Dis* 2002; 2 suppl 1: S46-75.

8. National Cancer Institute Common Toxicity Criteria (CTC). http://ctep.cancer.gov/reporting/ctc.html

9. van der Voort PH, van Hagen E, Hendrix G, van Gelder B, Bech JW, Pijls NH. Comparison of intravenous adenosine to intracoronary papaverine for calculation of pressure-derived fractional flow reserve. *Cathet Cardiovasc Diagn.* 1996;39:120-125.

10. Carlier SG, Di Mario C, Kern MJ, Serruys PW. Intracoronary doppler and pressure monitoring. In: Textbook of Interventional Cardiology. E. Topol. WB Saunders 1999. Chapter 40, P748.

11. Reiber JH, Serruys PW, Kooijman CJ, Wijns W, Slager CJ, Gerbrands JJ, Schuurbiers JC, den Boer A, Hugenholtz PG. Assessment of short-, medium-, and long-term variations in arterial dimensions from computer-assisted quantitation of coronary cineangiograms. *Circulation.* 1985; 71: 280-288.

12. Rother, R. P., Bell, L., Hillmen, P. Gladwin, M. T. The Clinical Sequelae of Intravascular Hemolysis and Extracellular Plasma Hemoglobin: A Novel Mechanism of Human Disease. *JAMA* 2005; 293: 1653-1662.

13. Schechter AN, Gladwin MT. Hemoglobin and the paracrine and endocrine functions of nitric oxide. *N Engl J Med* 2003; 348: 1483-1485.

14. Ritu Saxena, Annemarie D. Wijnhoud, Herwig Carton, Werner Hacke, Markku Kaste, Robert J. Przybelski, Kathleen N. Stern, and Peter J. Koudstaal. Controlled safety study of a hemoglobin-based oxygen carrier, DCLHb, in acute ischemic stroke. *Stroke.* 1999;30:993-996.

15. Minneci PC, Deans KJ, Zhi H. Hemolysis-associated endothelial dysfunction mediated by accelerated NO inactivation by decompartmentalized oxyhemoglobin. *J Clin Invest* 2005; 115: 3409-3417.

16. Schechter A. N., Gladwin M. T. Hemoglobin and the Paracrine and Endocrine Functions of Nitric Oxide. *N Engl J Med* 2003; 348:1483-1485.

17. Murray JA, Ledlow A, Launspach J, Evans D, Loveday M, Cocklin JL. The effects of recombinant haemoglobin on esophageal motor functions in humans; *Gastroenterology* 1995; 109: 1241-1248.

18. Schafer A, Wiesmann F, Neubauer S, Eigenthaler M, Bauersachs J, Channon KM. Rapid regulation of platelet activation in vivo by nitric oxide. *Circulation* 2004; 109: 1819-1822.

19. Olsen SB, Thang DB, Jackson MR, Gomez ER, Ayala B, Alving BM. Enhancement of platelet deposition by cross-linked hemoglobin in a rat endartherectomy model. *Circulation* 1996; 93: 327-332.

20. Rohlfs RJ, Bruner E, Chiu A, Gonzales A, Gonzales ML, Magde D, Magde MD Jr, Vandegriff KD, RM Winslow. Arterial Blood Pressure Responses to Cell-free Hemoglobin Solutions and the Reaction with Nitric Oxide, *J. Biol. Chem.*, 1998; 273: 12128-34.

21. Van Mieghem CAG, McFadden EP, de Feyter PJ, Bruining N, Schaar JA, Mollet NR, Cademartiri F, Goedhart D, de Winter S, Granillo GR, Valgimigli M, Mastik M, van der Steen AF, van der Giessen WJ, Sianos G, Backx B, Morel MAM, van Es GA, Zalewski A, Serruys PW. Noninvasive Detection of Subclinical Coronary Atherosclerosis Coupled With Assessment of Changes in Plaque Characteristics Using Novel Invasive Imaging Modalities, *JACC* Vol. 47, No. 6, 2006 March 21, 2006:1134–42.

22. Rother Russell P., Bell Leonard, Hillmen Peter, Gladwin Mark T. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin. A novel mechanism of human disease. *JAMA* 2005; 293: 1653-1662.

23. Kannan MS, Gulang S, Johnson DE. Nitric oxide: biological role and clinical uses. *Indian J Pediatr.* 1998;65:333-345.

24. Nafa K, Mason PJ, Hillmen P, Luzzatto L, Bessler M.. Deficiency of the GPI anchor caused by a somatic mutation of the PIG-A gene in paroxysmal nocturnal hemoglobinuria. *Cell.* 1993;73:703-711.

25. Navarro VJ, Senior JR. Current concepts: Drug related hepatotoxicity. *N Engl J Med* 2006; 354:731-739.

CHAPTER 27

PROOF-OF-CONCEPT TRIAL TO EVALUATE HAEMOGLOBIN BASED OXYGEN THERAPEUTICS IN ELECTIVE PERCUTANEOUS CORONARY REVASCULARISATION. RATIONALE, PROTOCOL DESIGN AND HAEMODYNAMIC RESULTS

EuroIntervention

Proof-of-concept trial to evaluate haemoglobin based oxygen therapeutics in elective percutaneous coronary revascularisation. Rationale, protocol design and haemodynamic results

Emanuele Meliga[1,5], MD; Pascal Vranckx[2,3], MD; Evelyn Regar[1,4], MD, PhD; Peter-Paul Kint[3], RN; Dirk J. Duncker[4], MD, PhD; Patrick W. Serruys[1]*, MD, PhD, FESC

1. Department of Interventional Cardiology, Thoraxcenter, Erasmus MC, University Medical Centre Rotterdam, The Netherlands; 2. Department of Cardiac Intensive Care & Interventional Cardiology. Virga Jesseziekenhuis, Hasselt, Belgium; 3. Cardialysis. Clinical Research Management & core Laboratories, Rotterdam, The Netherlands; 4. Experimental Cardiology, Thoraxcenter, Erasmus MC, University Medical Center Rotterdam, The Netherlands; 5. Department of Interventional Cardiology, S.G. Battista Hospital, Turin, Italy

All authors have no conflict of interest to declare.

KEYWORDS
HBOC-201, percutaneous coronary interventions, oxygen donor

Abstract

Aims: To test the hypothesis that intracoronary infusion of pre-oxygenated HBOC-201 during brief, total coronary artery occlusion would preserve left ventricular function.

Methods: Immediately following a successful PCI, the target coronary artery was occluded without ("dry occlusion") –or with– infusion of pre-oxygenated HBOC-201 distal to the stent via the guidewire shaft of an over-the-wire balloon for up to three minutes at an infusion rate of 48 ml/min. A cross-over design was applied. Early signs of myocardial ischaemia were evaluated by left ventricular pressure-volume loops and intracoronary ECG. A 12-lead Holter ECG was activated before the PCI and deactivated four hours after the study period. Primary endpoints were change in left ventricular relaxation indices and in the sum of ST segment deviations.

Results: None of the measured parameters differed significantly from their respective baseline values during HBOC-201 infusion. By contrast, ejection fraction (EF), cardiac output (CO) and minimal rate of LV pressure change (dP/dT_{MIN}) decreased significantly and the end diastolic pressure (EDP) and time constant of relaxation increased significantly during dry occlusions ($P<0.05$). The end diastolic pressure-volume relationship (EDPVR) at the fixed pressure level of 30 mmHg (V_{30}), an index of myocardial compliance, reflected greater myocardial stiffness during dry occlusions compared to occlusions with HBOC-201 infusion.

Conclusions: Intracoronary infusion of oxygenated HBOC-201 is capable of preserving left ventricular function, likely through maintenance of myocardial oxygenation. It is hypothesised, that in an acute setting, HBOC-201could serve as an oxygen bridge to reperfusion by PCI extending the "golden" time period during which permanent myocardial damage is unlikely.

* *Corresponding author: Thoraxcenter, Ba-583, 's Gravendijkwal 240, 3015RD, Rotterdam, The Netherlands*
E-mail: p.w.j.c.serruys@erasmusmc.nl

Introduction

HBOC-201 is a cell-free, endotoxin-free, glutaraldehyde-polymerised haemoglobin solution produced by chemical modification of bovine haemoglobin. Initially developed as an alternative to red blood cells for anaemic surgical patients, HBOC-201 has the ability to restore tissue oxygenation in persistently ischaemic tissue. By facilitating oxygen diffusion and convective oxygen delivery, HBOC-201 may act as a direct oxygen donor and increase oxygen transfer between red blood cells and between RBCs and tissues[1,2]. These mechanisms could improve tissue oxygenation[3], especially in post-stenotic areas that free plasma, but not RBCs, is capable of reaching. HBOC-201 can be stored at room temperature for a period of up to three years and does not require cross-matching.

Because HBOCs can deliver oxygen, they have been considered as an adjunct treatment in ACS. Studies conducted in animal models demonstrated that both the prophylactic (before induction of ischaemia) and late (after ischaemia onset) HBOC infusion are well tolerated and effective[4-8].

The safety and tolerability of HBOC up to 230 ml in low to moderate risk cardiac patients scheduled for elective PCI has recently been investigated in the COR-001 trial[9]. This study showed that intravenous HBOC-201 administration did not compromise autoregulation of coronary blood flow, despite the known vasoconstrictive properties of this drug, or myocardial function as assessed by the left ventricular stroke work. A transient increase in the mean arterial blood pressure (MAP) and systemic vascular resistance was observed, consistent with the purported nitric-oxide scavenging activity of the drug.

The present study is a first step towards establishing the efficacy and safety of oxygenated HBOC-201 in preserving myocardial function using PCI techniques to induce brief coronary artery occlusion in humans. Additional safety information regarding intra-coronary delivery of oxygenated HBOC-201 has also been collected.

Methods

Study design

The COR-0002 pilot trial is a single-centre, phase II, placebo-controlled, crossover, single-blind study conceived to test the hypothesis that HBOC-201 administration improves myocardial "oxygenation" and myocardial function during brief coronary occlusion. Enrolled subjects underwent coronary balloon occlusion, with and without oxygenated HBOC-201 intracoronary infusion (11-12 g/dl at 48 ml/min up to 3 min). The study was approved by the Medical Ethics Committee of the Erasmus Medical Centre (Rotterdam, The Netherlands) and was performed in accordance with the International Conference on Harmonisation of Good Clinical Practice (ICP/GCP) guidelines.

Patients

Patient inclusion and exclusion criteria are summarised in Table 1. In brief, patients were eligible for the study if they were admitted for either documented silent ischaemia, stable angina or unstable angina (Braunwald class I-IIIB)[10]. To optimise safety and size of the area at risk, eligibility was further constrained to patients with a target lesion in the proximal part of the left anterior descending coronary artery, in the absence of associated angiographically visible collateral vessels. Further, a successful index PCI, with focal stenting of the target lesion during the same cath lab session, was required prior to initiating the study period.

The pre-PCI standard 12-lead ECG recording corresponds to the baseline for quantitative dynamic analysis of ST changes over time during the study period. Written informed consent was obtained from all patients before the initiation of any study-specific procedures, including pre-treatment sedation.

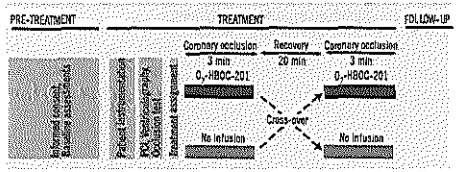


Figure 1. The COR-0002 trial was divided into three phases: a preparation period (pre-treatment phase), a treatment phase and a follow-up phase. The study period began after the lesion was successfully treated (PCI and stenting). Continuous 12-lead HOLTER ECG was recorded from pre-PCI to four hours after the study period ended (follow-up). PCI: percutaneous coronary intervention.

Study procedures

Data collection points and study design are depicted in Figure 1. All subjects were followed from study inclusion to hospital discharge. An independent physician was appointed to monitor safety and welfare of the study subjects and review the clinical events during the study period.

Concomitant treatment

Standard medications used in the management of subjects with ischaemic heart disease were not withheld per study protocol with the exception of analgesics. Use of analgesics was restricted as much as possible and were not administered immediately before study drug infusion.

PRE-TREATMENT PHASE

Laboratory testing, including haematology (haemoglobin, haematocrit, platelets and INR) and blood chemistry (creatinine, LDL, AST, ALT, amylase, troponin T, CK total and CK-mb), was performed at pretreatment baseline (within 24 hours of the study period) and eight hours post PCI. HBOC-201 was pre-oxygenated within 24 hours of the study period using a proprietary system designed and validated for this purpose (Figure 2).

Continuous 12-lead Holter monitoring. On arrival in the cath lab, the patient was connected to a continuous 12-lead Holter ECG recording device which was activated before the PCI and deactivated four hours after the study period. The Holter data were sent to an independent ECG core laboratory (Cardialysis, Rotterdam, The Netherlands) where ST segment changes over time

Table 1. Key inclusion/exclusion criteria.

Inclusion criteria
– Males or females between 18 and 80 years of age
– Stable angina pectoris (CCS- Class 1, 2, 3, 4) or unstable angina (Braunwald class I-III, B) or documented silent ischaemia.
– Baseline ECG with stable sinus rhythm and no signs of myocardial ischaemia, with no Q waves, bundle branch block or intra ventricular conduction disturbances.
– Normal left ventricular wall motion with preserved (ejection fraction ≥ 55%) systolic global left ventricular function.
– Non-occlusive stenosis, located in the proximal segments of the left anterior descending artery and/or circumflex artery or right coronary artery requiring PCI with coronary stenting.
– Secondary inclusion criteria to be assessed after completion of stenting procedure.
Key exclusion criteria
– Non-ST segment elevation myocardial infarction (patients with any troponin T elevation within the last 5 days).
– History or ECG evidence of prior myocardial infarction in the territory supplied by the vessel undergoing PCI, intraventricular conduction defects/baseline ST-segment abnormalities on the surface ECG.
– Moderate to severe aortic or mitral valve disease.
– Angiographically visible collateral vessels to the target vessel.
– Hypertension not adequately controlled by anti-hypertensive therapy at the time of study entry (> 140/100 mmHg).
– Uncompensated congestive heart failure or signs of pulmonary oedema.
– Significant haemodynamic compromise and/or cardiogenic shock requiring inotropic or pressor support.
– Known history of COPD with FEV_{1s} <1.0 L
– Serum creatinine > 1.6 mg/dL.
Secondary exclusion to be assessed upon completion of coronary stenting procedure
Active myocardial ischaemia
Coronary spasm
TIMI in treated vessel < 3
Any deterioration in subject's status between informed consent and randomisation, ie SBP > 180 mmHg, PCWP or LVEDP > 20 mmHg

CCS: Canadian Cardiovascular Society Scale; PCI: percutaneous coronary intervention

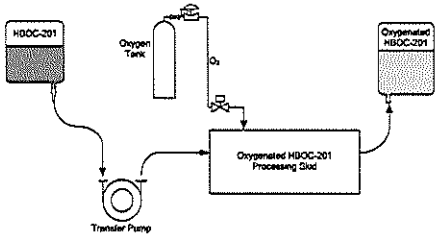


Figure 2. In vitro oxygenation system. In this closed circuit system, HBOC-201 is pumped across a liquid-gas exchange apparatus in which the gas side is supplied with a continuous stream of medical-grade oxygen. The exiting oxygenated HBOC-201 is collected into pre-sterilised bags at a concentration of 11-13 g/dl.

were analysed by an experienced, independent analyst who has no knowledge of the order of study treatments. ST-segment shift compared to baseline was analysed in the lead that demonstrated the most severe alterations as well as in all leads showing ST-segment changes ≥ 1 mm (at 60 ms after the J-point).

Patient instrumentation. Vascular access was obtained using the femoral approach with a standard Seldinger technique. Usually, a 6 or 7 Fr arterial sheath was selected. Prior to starting the PCI procedure, a conductance catheter was inserted into the left ventricle by an additional 8 Fr arterial sheath (details concerning the haemodynamic data acquisition are provided below in "Left ventricular haemodynamics"). A Swan-Ganz catheter was placed in the pulmonary artery via the femoral vein for cardiac output determinations by thermal and hypertonic saline (NaCl 10%) dilution methods.

INDEX PCI PROCEDURE PHASE

An index PCI procedure was performed according to standard institutional practices. All patients were pretreated with aspirin and clopidogrel (300 mg) 2-8 hours prior to the intervention. PCI procedural success was defined as successful stent deployment in the target lesion with a residual percent in-stent diameter stenosis of < 15% and TIMI 3 flow of the target vessel without the need for bypass surgery and in the absence of death.

THE STUDY PHASE

Upon successful completion of the index PCI procedure, a short over-the-wire (OTW) balloon (Helios 1.5, Goodman, Japan) was positioned inside the stent using a conventional 0.014 inch guidewire (Balance Middle Weight, Guidant, Indianapolis, IN, USA). The OTW balloon was used to temporarily re-occlude the stented segment and to perform the study-specific, selective intracoronary infusion. Before any study drug infusion, an occlusion test was performed with contrast injection through the guiding catheter to confirm that complete occlusion could be achieved. A conventional 0.014-inch guidewire (Balance Middle Weight, Guidant, Indianapolis, IN, USA) was inserted outside the OTW balloon, distal to the stent (in the "region of interest") to allow for continuous "online" intracoronary ECG monitoring (Figure 3). Printouts of these ECG recordings were collected and sent to the independent ECG core laboratory (Cardialysis, Rotterdam, The Netherlands).

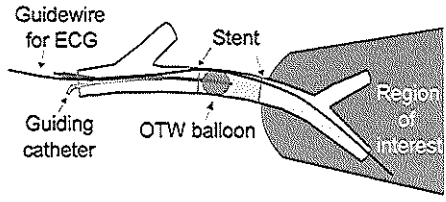


Figure 3. A short over-the-wire balloon was positioned inside the stented segment using a long conventional 0.014 inch guidewire (Balance Middle Weight, Guidant, Indianapolis, IN, USA). ECG signs of myocardial ischaemia were assessed by an intracoronary lead positioned in the guidewire shaft of the over-the-wire balloon catheter and placed distal to the stent in the region of interest. OTW: over-the-wire.

Study occlusion and fluid infusion: All subjects underwent two intrastent balloon occlusions (balloon inflation pressure=0.5 atm). During one occlusion, a continuous intracoronary infusion of pre-oxygenated HBOC-201, warmed to 37°C, was administered through the OTW lumen at a rate of 48 ml/min (maximum volume infused is 144 ml). HBOC-201 was warmed via an in-line clinical fluid warmer (Astotherm®plus, Model AP220S, Futuremed America, Inc., Granada Hills, CA, USA) positioned immediately proximal to the intracoronary OTW helios balloon catheter. HBOC-201 was contained within the sterile, high-pressure infusion line wrapped around the heating coil of the clinical fluid warmer. The infusion rate of 48 ml per minute was selected, based on the efficacy of intracoronary oxygenated HBOC-201 in swine subjected to simultaneous coronary occlusion. The infusion rate employed in this preclinical study was extrapolated to a corresponding rate in man after adjustment for differences in the average body weights of the animals and subjects of the COR-0002 trial.

The control occlusion period was performed similarly, but without infusion (termed "dry occlusion"). Subjects were assigned to receive pre-oxygenated HBOC-201 during the first occlusion period and no-infusion during the second period or vice versa. Each occlusion and infusion period lasted for up to three minutes. Three patients received oxygenated HBOC-201 during the first coronary occlusion and two patients received a dry occlusion as the first experimental intervention. Pre-determined criteria for premature interruption of the balloon occlusions were:

- ≥ 100% increase of left ventricular end-diastolic pressure (LVEDP) from baseline
- Sustained ventricular arrhythmias (ventricular tachycardia or ventricular fibrillation)
- Intolerable chest pain (angina)
- Significant hypertension (systemic blood pressure rise to > 180 mmHg)
- Significant LV dysfunction (EF decrease to less than 35%)

Once the balloon had been deflated and the infusion stopped, a "resting period" of 20 minutes followed for all recorded parameters to return to baseline (in particular LVEDP). The treatment period concluded after the second deflation, once all parameters had returned to their baseline values. A control angiogram was performed immediately after each balloon deflation to allow off-line quantitative coronary angiography (QCA)[11] of the region of interest.

Left ventricular haemodynamics

Left ventricular haemodynamic data were recorded before, during and after the procedure by online left ventricular pressure-volume signals obtained by a 7 Fr combined pressure-conductance catheter (CD Leycom, Zoetermeer, The Netherlands) introduced into the left ventricle via the femoral artery. The catheter was connected to a Cardiac Function Lab (CFL-512, CD Leycom, Zoetermeer, The Netherlands) for display and acquisition of pressure-volume loops. Parallel conductance and cardiac output were determined by multiple injections of hypertonic saline solution and thermodilution, respectively, in order to calibrate the volume signals of the conductance catheter. Data analysis was performed off-line by custom-made software. Cardiac function was quantified by cardiac output and stroke volume, stroke work, end-diastolic and end-systolic volume, LV ejection fraction, end systolic and end diastolic pressure, maximal and minimal rate of LV pressure change (dP/dtMAX and dP/dtMIN). The isovolumic relaxation period (defined as the period between the time point of dP/dtMIN and the time point where dP/dT reached 10% of the dP/dtMAX value) was analysed using phase-plot analysis and the time constant of relaxation (Tau) was then determined. The end diastolic pressure-volume relationship (EDPVR) was estimated using the method adopted by Klotz et al[12]. The change in diastolic distensibility was calculated by the relative left and rightward shifts of the EDPVR at the fixed pressure level of 30 mmHg (V30). Systemic haemodynamics were quantified by systolic, diastolic and mean systemic arterial pressure recorded every three minutes through the guiding catheter for the duration of the study period to investigate any possible hypertensive effects of HBOC-201 infusion.

Objectives

The main objectives of this study (Table 2) were early signs of myocardial ischaemia during intrastent balloon inflation defined as changes in left ventricular relaxation (Tau and dP/dT_{MIN}) and changes in the sum of ST segment deviations (assessed by continuous 12-lead Holter ECG monitoring) compared to baseline. Secondary objectives included changes in the cardiac performance measured by LV pressure volume loop analysis, clinical signs of myocardial ischemia and changes in coronary vascular tone measured by QCA.

Because of the crossover study design, it is not possible to make a direct comparison between treatment modalities (HBOC-201 vs. dry occlusion). However, it was possible to assess treatment safety

Table 2. Study endpoints.

Primary endpoints
The change in left ventricular relaxation indices (relaxation time constant Tau [ms] and pressure-half time [ms] as measured by left ventricle pressure-volume loop analysis) and the change in the sum of ST segment deviations (as assessed by continuous 12-lead Holter ECG monitoring) compared to baseline.
Secondary endpoints
– Left ventricular haemodynamics as assessed by left ventricle pressure-volume loops. Parameters taken into account are: - heart rate - left ventricle end-systolic pressure and volume, - left ventricle end-diastolic pressure and volume, - maximal and negative dP/dt (mmHg/s), - left ventricle ejection fraction (%), - left ventricle stroke work (mmHg.ml).
– The change of ST segment as recorded at intracoronary ECG measures during balloon inflation.
– The local (vasoconstrictive) effect of HBOC-201(r) on coronary artery diameters as assessed with off-line quantitative coronary analysis based on angiograms performed before and immediately after study drug infusions.
– Safety endpoints as measured by in-hospital occurrence of: - thrombotic events by: abrupt vessel closure (angiographic) - anaphylactic type of reactions by: clinical signs - life-threatening cardiac arrhythmias (sustained ventricular tachycardia, ventricular fibrillation, asystole, 2nd or 3rd degree atrial-ventricular block) as recorded by the 12-lead Holter ECG - any (serious) adverse events

from the haemodynamic responses, intracoronary and Holter 12-lead ECG monitoring and QCA measurements during the treatment period. Holter 12-lead ECG monitoring continued for four hours after conclusion of the study period and a 12-lead ECG was recorded at discharge or four days post treatment, whichever was earlier. Blood chemistry (LDH, ALT, AST, amylase, CK, CK-MB, troponin T) was collected 6-8 hours post-treatment for comparison to pre-index PCI baseline values. Additional safety endpoints included the in-hospital occurrence of adverse events.

Statistical analysis

Variables with normal distribution were analysed using parametric tests while variables with a non-normal distribution were analysed with non-parametric tests. Continuous variables are expressed as mean±SD or median ± inter-quartile range (IQR) and differences were compared using Student *t* test or Mann Whitney test. Categorical variables are expressed as counts and percentages.

All values were normalised in order to account for baseline variability. Normalisation was done by dividing each response to treatment (HBOC-infusion or dry occlusion) by the respective baseline. This method of normalisation was selected because it was an appropriate strategy to minimise the variability associated with differences in baselines between subjects. Differences were assessed by T- test or chi-square test. All statistical tests were two-tailed. All analyses were performed using SPSS version 12 statistical software (SPSS Inc., Chicago, IL, USA). A P value <0.05 was considered significant. Due to the descriptive nature of this study, no sample estimation was utilised.

Results

Subject baseline characteristics are described in Table 3. Patients (n=5) of mean age of 54.4±14 years underwent stent implantation for proximal (n=5) and/or mid LAD lesion (n=1) and were enrolled in the present study. Stent per patient ratio was 1.8±1.3. Diagnosis at admission was class II stable angina for all five patients. Hypertension was present in two patients, hypercholesterolaemia in three and familiar risk factor in one patient. No patient was diabetic. The mean ejection fraction (EF) was 66±10% and the mean EuroSCORE was 1.1±0.32%. Procedural and haemodynamic results are illustrated in Figures 4, 5 and 6. None of the measured haemodynamic parameters differed significantly from their respective baseline values during HBOC infusion. When data obtained during HBOC infusion and dry occlusion phases were compared, a statistical difference was shown for all systolic and diastolic performance indexes evaluated except dP/dTMAX. EF, CO and dP/dTMIN decreased significantly during dry occlusions from median values of 0.98 (IQR 0.09), 1 (0.06) and 0.99 (0.08) to 0.78 (0.22), 0.9 (0.16) and 0.85 (0.16), respectively. EDP and Tau

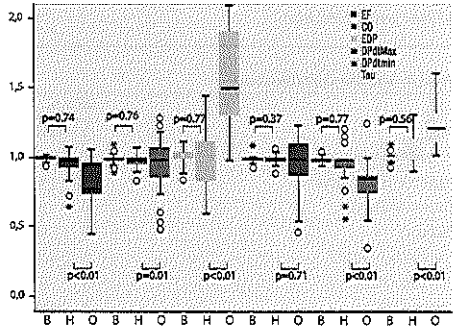


Figure 4. Box plot illustrating the changes in haemodynamics that occurred during HBOC infusion (H) and dry occlusion (O) compared to baseline values (B). Solid lines inside the boxes: median; box ends: IQR. Stars and circles: outsiders.

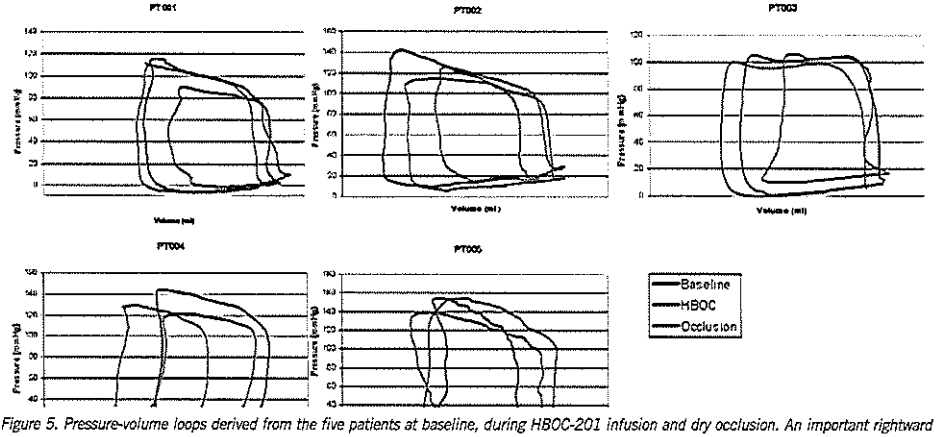


Figure 5. Pressure-volume loops derived from the five patients at baseline, during HBOC-201 infusion and dry occlusion. An important rightward shift of the PV loop occurred in all patients except PT005 during dry occlusion. By contrast, HBOC-201 infusion increased ESV and EDV in only one patient (PT004).

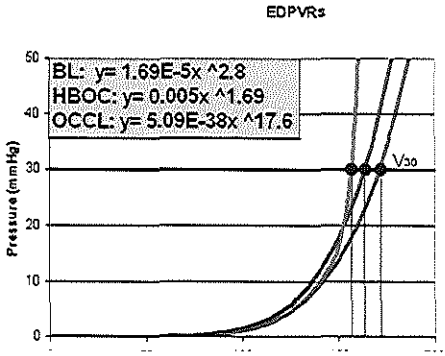


Figure 6. Mean EDPVR and V30 at baseline, during HBOC-201 infusion and dry occlusion.

Table 3. Baseline characteristics.

Age	54.4±14
Men	5 (100)
Arterial hypertension	2 (40)
Hypercholesterolaemia	3 (60)
Current Smoking	0 (0)
Diabetics	0 (0)
Familiar risk factor	1 (20)
Previous AMI	0 (0)
Previous PCI	1 (20)
Previous CABG	0 (0)
Previous cerebrovascular event	1 (20)
Stable angina	5 (100)
Class II	5 (100)
LVEF	66±10
Lesion location	
proximal LAD	5 (100)
mid LAD	1 (20)
Stent/patient	1.8±1.3
EuroSCORE	1.1±0.32

AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; LVEF: left ventricular ejection fraction; LAD: left anterior descending.
Data are number (%) or mean (±standard deviation).

increased significantly during dry occlusions from median values of 1 (0.39) and 1 (0.16) to 1.5 (0.71) and 1.21 (0.23), respectively. The change in dP/dTMAX was not statistically significant (from 1 (0.04) to 1 (0.28), p=0.71). During dry occlusion, an important rightward shift of the PV loop occurred in all patients but PT005, while during HBOC infusion, ESV and EDV did not increase with the exception of PT004. V30 decreased from 172 ml at baseline to 164 ml and 156 ml during HBOC infusion and dry occlusion, respectively (p=0.21).

Intrastent occlusions performed with infusion of pre-oxygenated HBOC-210 all lasted the intended three minutes duration; specifically, criteria for premature interruption of the inflation were never met. However, mean duration for dry occlusions was 2.13 ± 0.12 min and premature termination of the occlusion was necessary in all subjects. Table 4 identifies the reason(s) for terminating the dry occlusion in each patient.

Intracoronary ECG data were available in four out of five patients. Data from patient two (PT002) were considered not analysable by the independent core laboratory. ST segment changes are shown in Figure 7. During HBOC infusion, ST segment showed no significant changes from baseline while it was found to be significantly elevated during the dry occlusion phase in patients three, four and five. Of note, transthoracic ECG did not show any significant change both during the study phase and during the occlusion period.

Table 4. Reasons for premature interruption of dry occlusion phase.

	Premature (Y/N)	Time (min)	Main reason	Additional reason
PT001	Y	2.15	LVEF<35%	multiple extrasystoles
PT002	Y	2.05	EDP>20mmHg	multiple extrasystoles
PT003	Y	2.46	LVEF<35%	
PT004	Y	2	VT	
PT005	Y	2.31	Chest pain	multiple extrasystoles

LVEF: left ventricular ejection fraction; EDP: end diastolic pressure; VT: ventricular tachycardia

QCA of the arterial segment distal to the stent (Table 5) did not show major differences in reference vessel diameter (RVD), minimal lumen diameter (MLD) and diameter stenosis (DS) during infusion of HBOC compared to baseline values.

From a safety point of view, mean systolic blood pressure (SBP) increase during the HBOC infusion was 10.8±10.5 mmHg. SBP never reached the critical values defined prospectively for protocol-specified pharmacological intervention with nitrates and/or nifedipine. There were no noteworthy findings in the clinical chemistry parameters and no serious adverse events in any patient through the 4-day follow-up phase occurred.

Discussion

The main results of this study are: 1) Intracoronary infusion of oxygenated HBOC-201 maintained left ventricular haemodynamic status during total proximal LAD occlusion; 2) LV systolic and diastolic properties were not affected during HBOC-201 infusion while they significantly deteriorated during the dry occlusion; 3) intracoronary ECG showed no significant ST segment changes during HBOC infusion; 4) QCA indicated no conduit coronary vasoconstriction by the study drug; 5) HBOC-201 did not cause any adverse event or significantly alter blood chemistry parameters through the follow-up period.

The COR-0002 study was designed to test the hypothesis that pre-oxygenated HBOC-201 is capable of supporting myocardial metabolism and preserving function during total coronary occlusion in humans. The experimental design selected is a sequential intrastent angioplasty balloon inflation model with intracoronary infusion of pre-oxygenated HBOC-201 compared to the same occlusion with no infusion. Parameters of systolic and diastolic function and ST segment changes were measured to determine whether intracoronary delivery of oxygenated HBOC-201

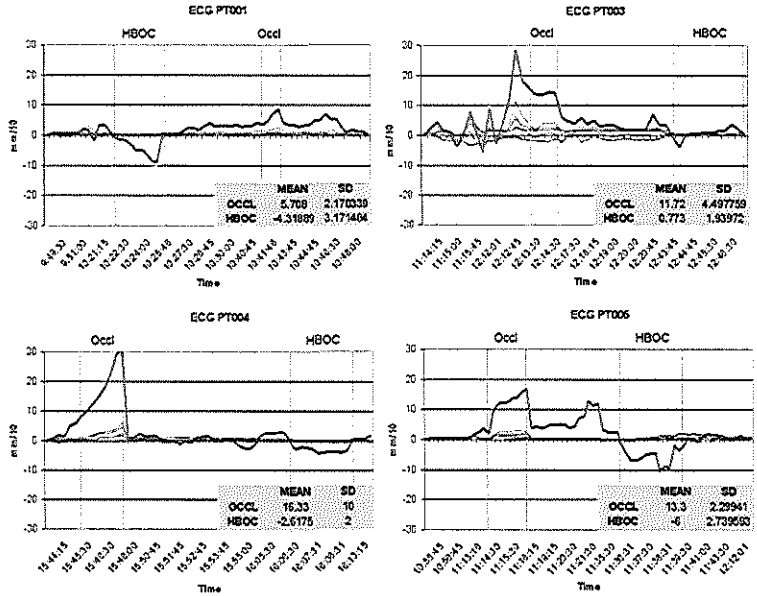


Figure 7. Intracoronary (red line) and surface (grey lines) lead changes in ST segments during the dry occlusion and HBOC-201 infusion interventions. During HBOC infusion, ST segment showed no significant changes from baseline while it was found to be significantly elevated during the dry occlusion phase in patients three, four and five.

Table 5. Quantitative coronary angiography (QCA) analysis.

	RVD (mm)			MLD (mm)			DS (%)		
PT	B	O	H	B	O	H	B	O	H
001	3.1	2.68	2.77	2.5	2.23	2.27	19	16	18
002	3.11	NA	3.23	2.44	NA	2.27	22	NA	30
003	2.28	2.23	2.07	1.7	1.86	2	25	17	3
004	2.22	2.23	2.22	1.94	1.97	1.84	13	12	17
005	2.86	2.67	2.28	1.95	1.76	1.78	32	34	22

PT: patient; RVD: reference vessel diameter; MLD: minimal lumen diameter; DS: diameter stenosis; B: Baseline; O: occlusion phase; H: HBOC infusion.

to myocardium at risk mitigates ischaemia. Local delivery of oxygenated autologous blood to the myocardium at risk through the central lumen of a dilated balloon catheter has previously proven to be safe, feasible and effective in patients in the setting of routine coronary angioplasty[13]. A one minute coronary occlusion and simultaneous infusion of blood at 60 ml/min reduced, but did not eliminate, arrhythmias and angina associated with control occlusions performed in the absence of infusion. Higher infusion rates tested only in vitro resulted in concerning levels of haemolysis and potassium release, events that are obviated with infusion of HBOC-201. As in this prior study, we selected a comparable, low-risk CAD patient population scheduled for elective PCI to assess the impact of intracoronary pre-oxygenated HBOC-201.

Percutaneous coronary angioplasty provides a unique opportunity to study the response of the human myocardium to brief periods of controlled ischaemia and reperfusion and the potential impact of study drugs. The present study involved repeated intracoronary balloon inflations with an intervening period of normal perfusion following successful deployment of a stent in an isolated proximal LAD stenosis. Acute recruitment of collateral vessels and ischaemic preconditioning may be a major confounding factor during successive balloon inflations in PTCA studies[5,14-16]. Previous studies have shown that if the duration of the first balloon inflation is longer than a "threshold" of ~ 60 to 90 seconds, indicators of myocardial ischaemia including chest pain severity, abnormalities of left ventricular regional wall motion and ST-segment elevation are attenuated during subsequent balloon inflations. These observations provide evidence of myocardial adaptation induced by the first period of ischaemia[17-19]. We anticipated this potential interference by using an alternating crossover clinical trial design. Furthermore, patients with angiographically evident collateral vessels supplying the area of interest were excluded[20].

The evaluation of early signs of myocardial ischaemia in this trial relied on continuous, invasive recording of PV loops, a technique able to provide detailed, reliable data on ventricular and myocardial performance[21] throughout the entire cardiac cycle. Isovolumic relaxation was evaluated by the peak rate of pressure decline (dP/dTMIN) and by the ventricular relaxation time constant Tau (τ). During the dry occlusion phase, early after balloon inflation, dP/dTMIN significantly decreased while τ significantly increased, both early indicators of myocardial ischaemia. During HBOC infusion, neither dP/dT nor Tau changed significantly from baseline values, suggesting HBOC substantially mollified the ischaemia otherwise induced by balloon inflation. Alterations of the isovolumic relaxation phase are the earliest and most sensitive signs of ischaemia-induced left ventricular dysfunction. Early asynchronous segment re-extension and regional non-uniformity also contribute to early onset and slower rate of ventricular pressure fall and might contribute to these diastolic disturbances[22]. Passive ventricular characteristics are well described by the end-diastolic pressure-volume relationship (EDPVR). Myocardial ischaemia often results in elevated left ventricular end diastolic pressures and in changes of the slope and position of the entire EDPVR[23-25]. Such shifts, when they occur, reflect a volume-independent increase in chamber stiffness.

In this series of subjects, LVEDP did not significantly increase during HBOC infusion, but increased continually in all subjects during the dry occlusion. Consistent with these results, V_{30} decreased more evidently during dry occlusion than during HBOC infusion, indicating greater myocardial stiffness during dry occlusion. It is interesting to note that the slope of the EDPVR remained unchanged during coronary occlusion with HBOC infusion compared to the dry occlusion phase, suggesting worsening of diastolic properties predominantly due to a reduction of myocardial distensibility. The pathophysiological mechanisms of this shift are not completely understood but it is thought to be due to an increased level of intracellular Ca++ during diastole[26] and to impaired myosin-actin cross-bridge inactivation secondary to elevated ADP concentrations[27-29]. Ventricular interactions and pericardial constraints may also contribute to these shifts.

Akin to diastolic function, systolic functions are importantly influenced by ischaemia. HBOC largely averted systolic dysfunction. Ejection fraction (EF) and stroke volume (SV), major indexes of the ejection phase properties, did not show significant variations from baseline during coronary occlusions with HBOC infusion while they were significantly reduced during the dry occlusion phase. These results were achievable despite the fact that the occlusions were performed in the proximal part of the LAD coronary artery which supplies a large "area at risk." Consistent with these results, dP/dT_{MAX}, commonly used as an isovolumic phase index of cardiac contractility, did not vary significantly from baseline during HBOC infusion suggesting preservation of systolic myocardial performance. It is also noteworthy, however, that the dP/dT_{MAX} values did not differ from baseline even after the onset of ischaemic conditions during dry occlusions, notwithstanding a wide IQR and outliers. It is likely that the shortness of the ischaemic period (criteria for premature interruption of the ischemic period were met in all subjects) and the load-dependence of dP/dT_{MAX} mitigated the real effect of ischaemia on the myocardium.

Early electrical signs of ischaemia in the area of interest were detected by using intracoronary ECG, a technique able to detect early signs of ischaemia with high sensitivity[30]. In this series of patients, HBOC infusion did not cause any significant alteration of the ST segment. The non-significant changes that occurred during the infusion phase, moreover, were only negative alterations (ST depression), suggesting that the myocardial wall was efficiently and protected by the drug. On the contrary, a significant ST elevation, a sign of transmural ischaemia, was detected in three out of four patients during dry occlusion phase. In PT001, the ST elevation did not reach significant levels most likely because the occlusion was interrupted relatively early, due to severe EF impairment (EF<35%) and the presence of multiple extra-systolic beats. In all patients, ST tended to remain elevated even after the balloon deflation while no ST alterations occurred during the resting periods following HBOC infusion.

In the COR-0001 clinical trial[9] the major side effect of the study drug was an increase of systemic vascular resistance, a mechanism not completely understood but possibly related to putative NO scavenging by HBOCs. Importantly, however, intravenously administered HBOC-201 had no effect on conduit or microvascular coronary tone in COR-0001 subjects. In the present study, QCA analysis demonstrated that the intracoronary infusion of HBOC also failed to alter conduit coronary artery tone, as indicated by a lack of effect on RVD, MLD and DS. The absence of coronary vasoconstriction, despite exposure to undiluted HBOC-201, further supports the potential utility of HBOC-201 in complicated patient subsets such as those with coronary artery disease.

Limitations

The present pilot study reports the results from a small series of five patients. Therefore, caution must be exercised in the interpretation of these data.

Although oxygenated HBOC-201 substantially preserved LV function, ameliorated or prevented cardiac arrhythmia and sharply reduced or eliminated coronary angina, treatment with study drug in this clinical trial was not fully optimised. In swine studies, intracoronary infusion of oxygenated HBOC-201 at 30 ml/min preserved approximately 80% of LV regional wall motion during coronary artery occlusion (unpublished data). Lower infusion rates yield proportionately less protection against coronary occlusion and higher infusion rates achieved full preservation of regional wall motion in swine. Extrapolating the 30 ml/min infusion rate in pigs to the average patient weight in the current clinical trial yields an infusion rate of 48 ml/min, the rate administered to subjects in this trial. Hence, higher intracoronary infusion rates based on individual body weights or coronary flows may have provided even greater LV protection against interruptions in coronary blood flow.

In summary, intracoronary oxygenated HBOC-201 represents a new category of pharmacologic strategies that may have utility in patients undergoing PCI. The results of this exploratory trial provide preliminary evidence that HBOC-201 can effectively preserve myocardial mechanical and electrical properties in the face of total coronary occlusion. This represents an important next step in the clinical development program for this product as a treatment for acute myocardial ischaemic syndromes. Future studies will be required

to determine if intracoronary and/or intravenous oxygenated HBOC-201 can enhance treatment efficacy in more complicated patient populations including STEMI and in cases where lesion access is difficult or when microvascular pathology contributes to low TIMI flow.

References

1. Page TC, Light WR, McKay CB, Hellums JD. Oxygen transport by erythrocyte/hemoglobin solution mixtures in an in vitro capillary as a model of hemoglobin-based oxygen carrier performance. *Microvasc Res* 1998;55(1):54-64.

2. Page TC, Light WR, Hellums JD. Prediction of microcirculatory oxygen transport by erythrocyte/hemoglobin solution mixtures. *Microvasc Res* 1998;56(2):113-26.

3. Standl T, Horn P, Wilhelm S, Greim C, Freitag M, Freitag U, Sputtek A, Jacobs E, Schulte am Esch J. Bovine haemoglobin is more potent than autologous red blood cells in restoring muscular tissue oxygenation after profound isovolaemic haemodilution in dogs. *Can J Anaesth* 1996;43(7):714-23.

4. Kasper SM, Walter M, Grune F, Bischoff A, Erasmi H, Buzello W. Effects of a hemoglobin-based oxygen carrier (HBOC-201) on hemodynamics and oxygen transport in patients undergoing preoperative hemodilution for elective abdominal aortic surgery. *Anesth Analg* 1996;83(5):921-7.

5. Matsubara T, Minatoguchi S, Matsuo H, Hayakawa K, Segawa T, Matsuno Y, Watanabe S, Arai M, Uno Y, Kawasaki M, Noda T, Takemura G, Nishigaki K, Fujiwara H. Three minute, but not one minute, ischemia and nicorandil have a preconditioning effect in patients with coronary artery disease. *J Am Coll Cardiol* 2000;35(2):345-51.

6. George I, Yi GH, Schulman AR, Morrow BT, Cheng Y, Gu A, Zhang G, Oz MC, Burkhoff D, Wang J. A polymerized bovine hemoglobin oxygen carrier preserves regional myocardial function and reduces infarct size after acute myocardial ischemia. *Am J Physiol Heart Circ Physiol* 2006;291(3):H1126-37.

7. Caswell JE, Strange MB, Rimmer DM, Gibson MF, Cole P, Lefer DJ. A novel hemoglobin-based blood substitute protects against myocardial reperfusion injury. *Am J Physiol Heart Circ Physiol* 2005;288(4):H1796-801.

8. Burmeister MA, Rempf C, Standl TG, Rehberg S, Bartsch-Zwemke S, Krause T, Tuszynski S, Gottschalk A, Schulte am Esch J. Effects of prophylactic or therapeutic application of bovine haemoglobin HBOC-200 on ischaemia-reperfusion injury following acute coronary ligature in rats. *Br J Anaesth* 2005;95(6):737-45.

9. Serruys PXS, Vranckx P, Slagboom T, Regar E, Meliga E, de Winter RJ, Heyndrickx G, Schuler G, van Remortel E, Dubé GP, Symons J. Haemodynamic effects, safety, and tolerability of haemoglobin-based oxygen carrier-201 in patients undergoing PCI for CAD. EuroInterv. 2008;3:600-609

10. Braunwald E. Unstable angina: a classification. *Circulation* 1989;80:410-414

11. Reiber JH, Serruys PW, Kooijman CJ, Wijns W, Slager CJ, Gerbrands JJ, Schuurbiers JC, den Boer A, Hugenholtz PG. Assessment of short-, medium-, and long-term variations in arterial dimensions from computer-assisted quantitation of coronary cineanglograms. *Circulation* 1985;71(2):280-8.

12. Klotz S, Hay I, Dickstein ML, Yi GH, Wang J, Maurer MS, Kass DA, Burkhoff D. Single-beat estimation of end-diastolic pressure-volume relationship: a novel method with potential for noninvasive application. *Am J Physiol Heart Circ Physiol* 2006;291:403-412.

13. Lehman KG, Atwood E, Snyder EL. Autologous blood perfusion for myocardial protection during coronary angioplasty: a feasibility study. *Circulation.* 1987;76:312-323

14. Deutsch E, Berger M, Kussmaul WG, Hirshfeld JW Jr, Herrmann HC, Laskey WK. Adaptation to ischemia during percutaneous transluminal coronary angioplasty. Clinical, hemodynamic, and metabolic features. *Circulation* 1990;82(6):2044-51.

15. Vaitkus PT, Miller JM, Buxton AE, Josephson ME, Laskey WK. Ischemia-induced changes in human endocardial electrograms during percutaneous transluminal coronary angioplasty. *Am Heart J* 1994;127(6):1481-90.

16. Lim R, Laskey WK. Ischemic preconditioning in unstable coronary syndromes: evidence for time dependence. *J Am Coll Cardiol* 1997;30(6):1461-5.

17. Cribier A, Korsatz L, Koning R, Rath P, Gamra H, Stix G, Merchant S, Chan C, Letac B. Improved myocardial ischemic response and enhanced collateral circulation with long repetitive coronary occlusion during angioplasty: a prospective study. *J Am Coll Cardiol* 1992;20(3):578-86.

18. Eltchaninoff H, Cribier A, Tron C, Derumeaux G, Koning R, Hecketsweiller B, Letac B. Adaptation to myocardial ischemia during coronary angioplasty demonstrated by clinical, electrocardiographic, echocardiographic, and metabolic parameters. *Am Heart J* 1997;133(4):490-6.

19. Airaksinen KE, Hulkuri HV. Antiarrhythmic effect of repeated coronary occlusion during balloon angioplasty. *J Am Coll Cardiol* 1997;29(5):1035-8.

20. Billinger M, Fleisch M, Eberli FR, Garachemani A, Meier B, Seller C. Is the development of myocardial tolerance to repeated ischemia in humans due to preconditioning or to collateral recruitment? *J Am Coll Cardiol* 1999;33(4):1027-35.

21. Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. *Am J Physiol Heart Circ Physiol* 2005;289(2):H501-12.

22. Leite-Moreira AF, Gillebert TC. The physiology of left ventricular pressure fall. *Rev Port Cardiol* 2000;19(10):1015-21.

23. Bronzwaer JG, de Bruyne B, Ascoop CA, Paulus WJ. Comparative effects of pacing-induced and balloon coronary occlusion ischemia on left ventricular diastolic function in man. *Circulation* 1991;84(1):211-22.

24. Barry WH, Brooker JZ, Alderman EL, Harrison DC. Changes in diastolic stiffness and tone of the left ventricle during angina pectoris. *Circulation* 1974;49(2):255-63.

25. Serizawa T, Carabello BA, Grossman W. Effect of pacing-induced ischemia on left ventricular diastolic pressure-volume relations in dogs with coronary stenoses. *Circ Res* 1980;46(3):430-9.

26. Kihara Y, Grossman W, Morgan JP. Direct measurement of changes in intracellular calcium transients during hypoxia, ischemia, and reperfusion of the intact mammalian heart. *Circ Res* 1989; 65(4):1029-44.

27. Tian R, Nascimben L, Ingwall JS, Lorell BH. Failure to maintain a low ADP concentration impairs diastolic function in hypertrophied rat hearts. *Circulation* 1997;96(4):1313-9.

28. Cave AC, Inwall JS, Friedrich J, Liao R, Saupe KW, Apstein CS, and Eberli FR. ATP synthesis during low-flow ischemia: influence of increased glycolytic substrate. *Circulation* 2000;101: 2090-2096.

29. Chen FC, Ogut O. Decline of contractility during ischemia-reperfusion injury: actin glutathionylation and its effect on allosteric interaction with tropomyosin. *Am J Physiol Cell Physiol* 20062;90:C719-C727.

30. Friedman PL, Shook TL, Kirshenbaum JM, Selwyn AP, Ganz P. Value of the intracoronary electrocardiogram to monitor myocardial ischemia during percutaneous transluminal coronary angioplasty *Circulation* 1986;74;330-339

SUMMARY AND CONCLUSIONS

Taking into consideration the published literature to date, the use of drug-eluting stents (DES) in patients with unprotected left main (ULM) coronary artery disease appears overall beneficial in comparison with bare metal stents (BMS). In particular, the use of DES is associated with significant reductions in target lesion revascularization, target vessel revascularization and MACE (major adverse cardiac events). In unspecified lesions, in-stent restenosis has been linked to the occurrence of acute coronary syndromes; but in the setting of left main restenosis, the risk of sudden cardiac death becomes a concern. Thus, the antiproliferative action of DES is of paramount importance in ULM lesions, and to date, DES should likely be recommended whenever percutaneous coronary interventions (PCI) for ULM is envisioned. Pooled analyses of registry data confirmed the early and mid-term safety and efficacy of DES implantation over BMS, under the premise that PCI is performed by experienced operators. Also, very-long-term follow-up of patients with ULM coronary artery disease treated with DES demonstrated a satisfactory rate in both single and composite outcomes. The progressive reduction of adverse events over time suggests

that DES are persistently effective. When PCI is performed electively, the event-free survival over a period of 3 years is excellent. This is independent of lesion location, stenting technique or type of drug-eluting stent used. When PCI is performed emergently, the favourable long-term clinical outcomes are hampered by lower event-free survival at shorter term follow-up.

It is interesting to note that in the in diabetic population with unprotected left main coronary artery disease the efficacy of DES is significantly influenced by the use of insulin. In fact, adverse outcomes comprising cardiac death, myocardial infarction, need of re-intervention and MACE was significantly increased in patients with insulin-dependent diabetes mellitus. The safety profile of drug-eluting stents appeared overall consistent with what has been reported in recent trials and registries focusing on selected patient/lesion subsets. The incidence of definite acute, sub-acute, late and very late stent thrombosis was low and not significantly related to cardiac death.

Notwithstanding the encouraging results obtained with DES for the treatment of ULM coronary artery disease, current guidelines still recommend surgical revascularization as the primary procedure. In all major institutions, current standard approach to patients presenting with significant ULM coronary artery disease is to have them evaluated by both interventional cardiologists and cardiac surgeons and to reach the decision to opt for PCI or surgery by consensus, on the basis of hemodynamic conditions, vessel / lesion characteristics, the presence of comorbidities and patient and/or referring physician preferences.

The results of the recently published SYNTAX trial represent a milestone and certainly will be taken into consideration in the upcoming guidelines. Guidelines are dynamic and in constant flux and have to be updated according to new evidences coming from clinical experience.

New-generation DES approved for clinical use, new technical strategies, new adjuvant therapies performed in the cath-lab, and prolonged dual antiplatelet treatment have significantly decreased the risk of adverse events (including late in-stent thrombosis), making PCI a safe and effective alternative to surgery in several high-risk subsets of patients.

In the context of chronic total occlusions both sirolimus-eluting stents and paclitaxel eluting stents have now been reported to be correlated with improved long-term clinical and angiographic outcomes compared with their BMS counterparts. Several studies reported high procedural success rates (particularly evident using the retrograde approach), single digit restenosis rates and no increase in stent thrombosis or late occlusion after DES implantation. Good clinical results were observed also in chronically occluded saphenous vein grafts. Though the benefit of DES in this lesion subset has not been formally evaluated (SVG lesions have been excluded from randomized trials), the available data coming from observational studies are encouraging. Remaining issues are the long-term safety and efficacy of DES in SVG lesions, considering that long-term events frequently result from the progression of other lesions in the vein. Regardless of the future progress in this field, we think that DES treatment currently is the best approach for SVG lesions. Despite extensive real-life use of DES in patients with multivessel disease, we cannot deny that sufficient data are still lacking. Rather than looking at the incidence of new revascularizations, which may be considered an acceptable "side effect" of any PCI strategy compared with CABG, we need to demonstrate equivalency or superiority in terms of MI and death evaluated no earlier than 5 years.

Coronary artery disease aside, advances in cardiovascular interventional techniques have allowed percutaneous treatment of conditions that either previously required open operations or have not been amenable to treatment.

Hypertrophic obstructive cardiomyopathy is a relatively common condition (prevalence of around 1 in 2000 persons) . The traditional method for the management of these patients has been the use of beta-blockers or calcium channel blockers, dual chamber pacing or surgical ventricular septal myectomy. Over the last decade, percutaneous approach to treatment of outflow tract gradient by ablating or creating a controlled infarction of the ventricular septum, has also been shown to be safe and effective. Percutaneous transluminal septal myocardial ablation (PTSMA) as well as septal coil embolization acutely reduce systolic function and improve diastolic function, maintaining cardiac output and stroke work. At long-term follow-up, the effects on general haemodynamics improve; in fact, while the LV–aortic gradient remaines low and active and passive LV diastolic properties are stable, myocardial contractility and systolic funcion improve. The indications for performing PTSMA are still being defined. Up to date, this novel technique may be a particularly attractive alternative in the elderly or those who because of significant co-morbidities cannot undergo /are refused by surgeons.

The enormous improvements in PCIs led to excellent rates of survival after an acute myocardial infarction. This increase has lead to a concomitant increase in the prevalence of post-infarction heart failure (HF) with at least a third of patients manifesting HF symptoms within a year. Currently, this increase is attributed both to limited efficacy of pharmacological agents at reducing left ventricle remodelling and HF exacerbations , and to underutilization of these drugs in general practice. Finally, post-infarction HF patients are surviving longer, in part because of a wider use of implantable cardioverter defibrillators. With the awareness that both

tissues and bone marrow (BM) contain undifferentiated immature 'stem' cells normally used to replenish body tissues throughout life , and that these cells can be harvested and delivered to sites of injury, a new therapeutic option has emerged: the transplantation of stem or progenitor cells for functional repair or even regeneration of vasculature, acutely injured and/or failing myocardium or previously irreversibly damaged heart – giving hope for cell-mediated prevention, treatment and possibly even cure of CVD. Trials performed to date have focused on the use of BM-MNCs, EPCs, MSCs and other cells throughout the continuum of cardiovascular disease, from advanced coronary atherosclerosis to end-stage HF, with the most patients treated following AMI. Three recent meta-analyses suggest that BM-MNCs provide statistically significant yet small (in clinical terms) benefit when administered post-AMI. However, on close examination of individual studies, the outcomes are discrepant. Whether the discrepancies represent differences in disease context, patient population, cell type and dose or some other factors remains to be resolved. In other words, 7 years after the initiation of the first study we still have as many (or more) questions as answers.

Among the variety of cells studied, autologous skeletal myoblasts are one of the most encouraging cell sources for cardiac repair. They are of their autologous origin, the ability to be amplified in vitro, and have high proliferative potential resistance to ischaemia and preclinical efficacy. These characteristics have led clinical investigators to evaluate the effect of transplanted autologous myoblasts in patients with post-infarction heart failure. Myoblasts differentiate into myotubes and maintain muscle properties when transplanted into an infarct area. The direct contribution

of these engrafted cells in improving systolic function was noticed in several studies that indicated a

positive effect of skeletal myoblasts on myocardial contractility lasting over time and correlating with the number of implanted cells.

Recently it has been shown that adipose tissue, in addition to committed adipogenic, endothelial progenitor cells and pluripotent vascular porgenitor cells, contains multipotent cells, similar to MSCs. ADSC have extensive proliferative capacity, are able to undergo differentiation along both mesenchymal lineages and non-mesenchymal lineages, are known to secrete a large number of angiogenesis-related cytochines and display and immunoprivileged behavior.

This finding has generated major interest because, in contrast to bone marrow, large quantities of adipose tissue can be easily harvested with minimal morbidity, making it an appealing source for cell therapy. The APOLLO trial will provide important data about the safety and efficacy of these cells in humans, providing an essential insight on what could be their role in the treatment of cardiovascular disease.

SAMENVATTING EN CONCLUSIES

In de tot op heden gepubliceerde literatuur lijkt het gebruik van geneesmiddelafgevende stents (*Drug Eluting Stents*, DES) bij patiënten met een aandoening van de linker hoofdcoronair over het algemeen gunstiger in vergelijking met normale metalen stents (*Bare Metal Stent*, BMS). Het gebruik van DES is met name geassocieerd met een significante afname van target laesie revascularisatie, target vaat revascularisatie en MACE (*major adverse cardiac events: ernstige cardiale gebeurtenissen*). In ongespecificeerde laesies wordt restenose van de stent in verband gebracht met het optreden van een acuut coronair syndroom; in de setting van linker hoofdrestenose is het risico op plotse hartdood echter zorgwekkend. De antiproliferatieve werking van DES is daarom van enorm belang bij ULM (*unprotected left main coronary= onbeschermde linker hoofdcoronair*) laesies. Tot op heden moet DES waarschijnlijk worden aanbevolen wanneer percutane coronaire interventies (PCI) voor ULM worden gepland. Gepoolde analyses van registratiedata bevestigden de gunstiger korte- en middellange termijnveiligheid en -werkzaamheid van DES implantatie in vergelijking met BMS, mits de PCI door een ervaren chirurg uitgevoerd wordt. Tevens toonde de zeer langetermijn follow up van patiënten met ULM coronarialijden die met DES waren behandeld bevredigende enkelvoudige en samengestelde resultaten. De progressieve afname van bijwerkingen in de loop van de tijd suggereert dat de effectiviteit van DES persisteert. Wanneer electieve PCI wordt verricht, is de incidentvrije overleving over een periode van 3 jaar uitstekend. Dit is onafhankelijk van laesielocatie, stentingtechniek of type geneesmiddelafgevende stent dat gebruikt wordt. Indien in spoedgevallen PCI wordt verricht, worden de gunstige langetermijn klinische resultaten verstoord door een lagere incidentvrije overleving bij kortere termijn follow up.

Interessant hierbij is dat in de diabetespopulatie met onbeschermde linker hoofdcoronairaandoening de effectiviteit van DES significant beïnvloed wordt door het gebruik van insuline. De negatieve uitkomsten zoals hartdood, myocardinfarct, noodzaak voor re-interventie en MACE waren zelfs significant verhoogd bij patiënten met insulineafhankelijker diabetes mellitus. Het veiligheidsprofiel van geneesmiddelafgevende stents bleek over het algemeen overeen te komen met de rapportage in recente trials en registraties van geselecteerde patiënt/laesie subsets. De incidentie van duidelijke acute, subacute, late en zeer late stenttrombose was laag en niet significant gerelateerd aan hartdood.

Ondanks de bemoedigende resultaten met DES voor de behandeling van ULM coronarialijden, wordt in de huidige richtlijnen operatieve revascularisatie nog steeds als primaire procedure geadviseerd. In alle grote instellingen is evaluatie door interventiecardiologen en hartchirurgen de huidige standaardbenadering van patiënten met significant ULM coronarialijden, waarbij wordt getracht consensus te bereiken over ofwel PCI ofwel een operatie, op basis van de hemodynamische toestand, vaat/laesie eigenschappen, de aanwezigheid van co-morbiditeit en de voorkeur van de patiënt en/of arts.

De resultaten van de recent gepubliceerde SYNTAX trial betekenen een mijlpaal en zullen zeker in overweging worden genomen in de nieuwe richtlijnen. Richtlijnen zijn dynamisch en constant in beweging en moeten volgens de nieuwste inzichten uit klinische ervaring worden bijgewerkt.

Nieuwe generatie DES die goedgekeurd zijn voor klinisch gebruik, nieuwe technische strategieën, nieuwe adjuvans therapieën in het cath-lab, en langdurige duale antiplaatjes behandeling hebben het risico op bijwerkingen (inclusief late stenttrombose) significant verlaagd, waarmee PCI een veilig en effectief alternatief is voor operatie in verscheidene hoogrisico subsetspatiënten.

Sirolimus-afgevende stents en Paclitaxel-afgevende stents correleren beide in de context van chronische totale occlusies met verbeterde langetermijn klinische en angiografische resultaten vergeleken met hun BMS-tegenpolen. Verscheidene studies meldden hoge procedurele succescijfers (met name evident bij de retrograde benadering), zeer lage restenosecijfers en geen toename van stenttrombose of late occlusie na DES implantatie. Er werden eveneens goede klinische resultaten waargenomen in chronisch geoccludeerde implantaten in de vena saphena. Hoewel het gunstige effect van DES in deze laesie subset niet formeel is geëvalueerd (SVG laesies zijn van gerandomiseerde trials uitgesloten), zijn de beschikbare data uit observatiestudies bemoedigend. Resterende kwesties zijn de langetermijnveiligheid en -werkzaamheid van DES in SVG laesies, waarbij in overweging moet worden genomen dat langetermijn incidenten vaak het gevolg zijn van de progressie van andere laesies in de ader. Ongeacht de toekomstige vooruitgang op dit gebied, denken wij dat DES behandeling op dit moment de beste benadering is voor SVG laesies. Ondanks het uitgebreide gebruik in de praktijk van DES bij patiënten met multivaataandoeningen, valt niet te ontkennen dat er nog onvoldoende gegevens beschikbaar zijn. In plaats van ons te richten op de incidentie van nieuwe revascularisaties, die een acceptabele bijwerking genoemd kunnen worden van een PCI strategie in vergelijking met CABG, moeten we de gelijkwaardigheid of superioriteit wat betreft myocardinfarct en overlijden na 5 jaar aantonen.

De vooruitgang in de cardiovasculaire interventionele technieken heeft het mogelijk gemaakt aandoeningen die eerder via open operaties werden behandeld of niet behandeld konden worden nu percutaan te behandelen.

Hypertrofische obstructieve cardiomyopathie is een relatief veel voorkomende aandoening (met een prevalentie van ongeveer 1 op de 2000 personen). De traditionele methode voor de behandeling van deze patiënten was het gebruik van bètablokkers of calciumkanaalblokkers, duale kamerpacing of operatieve ventriculaire septale myectomie. In het afgelopen decennium is gebleken dat ook een percutane benadering als behandeling van outflow tract gradiënt door ablatie of induceren van een gecontroleerd infarct van het ventriculaire septum veilig en effectief is. Percutane transluminale septum myocard ablatie (PTSMA) en septaal coil embolisatie verlagen acuut de systolische functie en verbeteren de diastolische functie, waarbij de cardiale output en stroke work blijven behouden. Bij langetermijn follow up verbeteren de effecten op de hemodynamica. Terwijl de LV aorta gradiënt laag blijft, en de actieve en passieve LV diastolische eigenschappen stabiel blijven, verbeteren de myocardiale contractiliteit en systolische functie. De indicaties voor het verrichten van PTSMA moeten nog worden vastgesteld. Deze nieuwe techniek kan in het bijzonder aantrekkelijk zijn voor ouderen of patiënten met

significante co-morbiditeiten die geen operatie kunnen ondergaan of die door de chirurg worden geweigerd.

De enorme verbeteringen van PCIs hebben tot een uitstekende overleving na acuut myocard infarct geleid. Deze stijging heeft geleid tot een gelijktijdige stijging van de prevalentie van postinfarct hartfalen, waarbij tenminste eenderde van de patiënten binnen een jaar symptomen van hartfalen (HF) vertonen. Deze stijging wordt nu toegeschreven aan zowel de beperkte effectiviteit van farmacologische middelen in het verlagen van de remodellering van de linker ventrikel en HF exacerbatie, en het ondergebruik van deze geneesmiddelen in de algemene praktijk. Tot slot overleven postinfarct HF patiënten langer, deels vanwege een breder gebruik van implanteerbare cardioversie defibrillatoren. Met de kennis dat zowel weefsels als beenmerg (BM) ongedifferentieerde onvolwassen 'stam'cellen bevatten die normaal gebruikt worden om tijdens het leven de lichaamsweefsels aan te vullen, en dat deze cellen geoogst en geplaatst kunnen worden in gebieden met letsel, is een nieuwe therapeutische optie ontstaan: de transplantatie van stam- of progenitorcellen voor het functionele herstel of zelfs de regeneratie van vasculatuur, acuut letsel aan en/of falend myocard of een eerder irreversibel beschadigd hart - hoopgevend voor celgemedieerde preventie, behandeling en mogelijk zelfs genezing van cardiovasculaire aandoeningen. De trials die tot op heden zijn verricht concentreerden zich op het gebruik van BM-MNC (beenmerg mononucleaire cel), EPC (endotheliale progenitorcel), MSC (multipotente stamcellen) en andere cellen in het continuüm van de cardiovasculaire ziekte, van gevorderde coronaire atherosclerose naar eindstadium HF, waarbij de meeste patienten een acuut myocardinfarct hadden doorgemaakt. Drie recente meta-analyses suggereren dat BM-MNC statistisch significante doch gering (in klinische termen) gunstig effect hebben bij toediening na acuut myocardinfarct. Bij een nauwkeurig onderzoek van de individuele studies zijn de resultaten uiteenlopend. Of de discrepanties door verschil in ziektecontext, patiëntpopulatie, celtype en dosis of andere factoren worden verklaard moet nog worden uitgezocht. Met andere woorden, 7 jaar na de aanvang van de eerste studie hebben wij nog steeds evenveel (of meer) vragen dan antwoorden.

Onder de diverse cellen die onderzocht zijn, zijn autologe skelet myoblasten een van de meest bemoedigende celbronnen voor cardiale reparatie. Zij zijn van autologe oorsprong, kunnen in vitro worden geamplificeerd, en hebben hoge proliferatieve potentiële weerstand tegen ischemie en preklinische effectiviteit. Deze eigenschappen hebben klinisch onderzoekers ertoe gebracht het effect te onderzoeken van getransplanteerde autologe myoblasten in patiënten met postinfarct hartfalen. Myoblasten differentiëren in myotubuli en behouden spiereigenschappen wanneer zij getransplanteerd worden in een geïnfarcteerd gebied. De directe bijdrage van deze geïmplanteerde cellen wat betreft de verbetering van de systolische functie werd opgemerkt in verscheidene studies die een positief effect toonden van skeletmyoblasten op myocardiale contractiliteit dat in de tijd aanhoudt en correleert met het aantal geïmplanteerde cellen.

Recent is aangetoond dat adipeus weefsel, naast de gecommitteerde adipogene endotheliale progenitorcellen en pluripotente vasculaire progenitorcellen, multipotente cellen bevat, gelijk aan MSCs. ADCS (*Adipose Tissue Derived Cells*) hebben uitgebreide proliferatieve capaciteit, zijn in staat te differentiëren langs beide mesenchymale lijnen en non-mesenchymale lijnen, staan erom bekend een groot aantal angiogenese-gerelateerde cytokines uit te scheiden en tonen een *immune privileged* gedrag.

Deze bevinding heeft grote belangstelling gewekt, omdat, in tegenstelling tot beenmerg, grote hoeveelheden adipeus weefsel eenvoudig kunnen worden geoogst met minimale morbiditeit, waarmee het een aantrekkelijke bron voor celtherapie wordt. De APOLLO trial levert belangrijke data over de veiligheid en effectiviteit van deze cellen bij de mens, en levert daarmee een wezenlijk inzicht van wat de rol kan zijn in de behandeling van cardiovasculaire aandoeningen.

CURRICULUM VITAE

Name
Emanuele Meliga

Date of birth
18-08-1978

Place of birth
Chivasso (Turin) - Italy

Nationality
Italian

Professional address
Department of Cardiology, Degli Infermi Hospital, Via Caraccio 5, 13900 Biella, Italy

Department of Cardiology, S. Giovanni Battista Hospital, corso Bramante 60, 10126 Turin, Italy.

Telephone
Mobile: 0039 338 80 65 081 (after 6 p.m. CET)

emeliga@gmail.com

An experienced Physician specialized in cardiology. Extensive knowledge relative to percutaneous coronary interventions, left-main coronary artery disease, cardiac physiology, left ventricular haemodynamics and cell therapy. In addition, I have fair expertise as trialist. I am a published author, and have written extensively on percutaneous interventions in high risk patients.

Educational- and clinical experience, research training

July 1997	: High School diploma (scientific lyceum).
Oct 1997	: Medical school, University of Turin (Italy).
July 2000/Jan 2001	: Rotations in internal medicine, University of Turin (Italy).
Jan.2001/Aug.2001	: Rotation in Cardiology, University of Turin (Italy).
Aug.2001/Jan.2002	: Rotation in the intensive care and vascular surgery. University of Turin (Italy).
Jan.2002/July 2003	: Rotation in Cardiac surgery and post-operative care. University of Turin (Italy).
July 2003	: Medical degree, summa cum laude (110/110 cum laude), Dux of class of 360 candidates, University of Turin (Italy).
October 2003	: Professional license as MD: member of the "albo dei medici-chirurghi e degli odontoiatri di Torino".
Jan.2004	: Specialization school: Department of Cardiology. Prof. Trevi, University of Turin (Italy).
Aug.2005/July 2006	: CCU –intensive care unit- Department of Cardiology. Dr. Marra. S. Giovanni Battista Hospital, Turin
Aug. 2006/April 2008	: Department of Interventional cardiology, Thoraxcentre, Prof. Serruys, Erasmus University of Rotterdam (Netherlands).
Dec 2007	: Certification as Cardiologist in Italy, summa cum laude.
April 2008	: Interventional Cardiology, San Giovanni Battista Hospital, Turin
April 2009	: Interventional Cardiology, Degli Infermi Hospital, Biella

Professional Society Memberships

European Society of Cardiology (ESC) 2006 to present
Italian Federation of Cardiology (FIC) 2005 to present
National Association of Cardiologists (ANMCO) 2005 to present

Employment Experience

2003: factory doctor (L'OREAL)
2004/2006: on call physician, private institution (casa di cura Cellini, Turin).
2004/2006: University Cardiology ward, S. Giovanni Battista Hospital, Turin.
2005/2006: on-call general practitioner.
2006/2008: Interventional cardiology dept., international fellow, PhD student, Thoraxcentre (NL).
2007/2008: Supervisor cardiologist, Research core lab, Cardialysis (NL)
2008: staff, Interventional Cardiology, San Giovanni Battista Hospital, Turin

Other Certifications

1998: Basic life support (BLS and BLS-D)
1999: Pre-Hospital Trauma Life Support (PHTLS)
2002: Advanced Medical Life Support (AMLS)
2005: Advanced Life Support (ALS)

Language spoken

Italian (native speaker)
English (proficiency)

Extracurricular Activities

Outside Interests: modern art, music, technology, scuba diving, photography, travels
Special Qualifications: Licensed Dive Master in 2002