TOWARDS OPTIMALIZATION OF CLINICAL OUTCOME AFTER PALMAZ SCHATZ CORONARY STENT IMPLANTATION

Naar optimalisatie van het klinisch resultaat van Palmaz Schatz coronaire stent implantatie

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof. Dr. P.W.C. Akkermans, M.A
en volgens besluit van het College van Dekanen.

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PROMOTIECOMMISSIE

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To my wonderful father, for giving all efforts to guide his freebooting son through his school years and who desperately tried to teach me that in mathematics , a "zero" was another "zero" than the one I knew from daily practice (zero="nothing" thus worthless and as a consequence neglectable under all circumstances... also in calculations).

To my dear mother for always being there.

To my beloved Marion, for enthousiastically going through all the plans we have in mind.

CONTENTS

CHAPTER 1

INTRODUCTION

INTRODUCTION

Since the first implantation of a Palmaz Schatz coronary stent in our department, in January 1990, we were confronted with both the beneficial and detremental properties of the device. We experienced that this stent was of great value in stabilizing patients with an occlusive dissection after balloon angioplasty (PTCA) [chapter 2.1 and 2.2] and we shared the opinion that the stent had the potential to reduce restenosis after balloon angioplasty, as was demonstrated later in the Benestent-I (1) and the STRESS (2)- studies. Because of its thrombogenicity, we adhered to the stringent anticoagulation regimen, which was advised to prevent stent thrombosis (3). Despite this strategy, stent thrombosis could not be prevented in the bailout situation (chapter 2.2) and, to a lesser extent, in the ideal study population, such as defined in the Benestent-I study (chapter 2.3 and 3.1). The combination of antiplatelet and anticoagulant therapy also resulted in a high incidence of entry-site related bleeding complications (chapter 2.2, 2.3 and 3.1).

In the course of 5 years, optimalization of clinical outcome after coronary stenting was explored in 5 directions:
[1] 1991-1992: Improvement of stent implantation technique by intravascular ultrasonic guidance
[2] 1991-1992: Improvement of anticoagulation monitoring by prothrombin fragment F1+2 assessment.
[3] 1991-1992: Improvement of local hemostasis and anticoagulation by application of collagen plugs.
[4] 1992-1995: Selection of a safer entrysite.
[5] 1994-1995: Implantation of non-thrombogenic stents.

[1] Improvement of stent implantation technique by intravascular ultrasonic guidance.
The risk for subacute stent thrombosis is reduced when larger final stent diameters are obtained (4,5,6). Although the angiographic appearance after stenting may be acceptable, stent expansion can be incomplete, when assessed with intravascular ultrasound (IVUS).
Stent dilatation with larger balloons at high inflation pressures does result in improved stent expansion (7). Since the Palmaz Schatz stent, incorporated in the prefabricated Stent Delivery System (SDS), is mounted on a compliant low pressure- balloon, we postulated that the stent could not be properly expanded after initial deployment with this SDS.
In the early years of stent experience, we compared stent expansion with IVUS after delivery with the SDS and after high pressure inflations with less compliant balloon material (chapter 4.1).

[2] Improvement of monitoring of anticoagulation by assessment of prothrombin fragment F1+2.
At the same time attention was focused on the importance of optimal anticoagulation to prevent stent thrombosis. From Swars et al. (8) and Hafner et al. (9) came promising news on the assessment of prothrombin fragment F1+2, as specific markers for impending stent thrombosis. In *retrospective* studies a rise of F1+2 was detectable in patients who developed stent thrombosis. By giving additional heparin if a rise in F1+2 was detected, stent thrombosis could be prevented (9).
However, administration of extra heparin, also in patients with Activated Partial Thromboplastin Times (APTT) within the therapeutic range, may further increase the risk of bleeding complications. Therefore, we performed a *prospective* study, to explore the practical value of this assessment by establishing the relation between prothrombin fragment F1+2-levels and the occurence of subacute thrombosis (chapter 4.2).

[3] Improvement of local hemostasis and anticoagulation by application of collagen plugs at the puncturesite.
Ernst et al. (10) and Sanborn et al. (11) reported on the value of collagen plugs, percutaneously inserted at the puncturesite after coronary angiography and PTCA.
These promising results, stimulated us to explore the value of this hemostatic device in the prevention of bleeding complications at full heparinization after coronary stenting (chapter 4.3).

[4] Selection of a safer entrysite.
In 1992, 6 French (F) guiding catheters became commercially available on a larger scale. By combining these guiding catheters with miniaturized balloon catheters, having a low profile even at larger balloon diameters, PTCA could be performed for a wide range of coronary artery sizes. As a prerequisite for PTCA through 6F guiding catheters, we considered the preservation of the possibility to offer the patient the same standard bailout techniques (perfusion balloons and stents), in case of a PTCA complication. We performed a study on the elective use and on emergency use of perfusion balloons as well as stents through 6F guiding catheters (chapter 4.4.1 and 4.4.2).
Based on work of Campeau, who reported in 1989 on the feasibility of transradial artery coronary angiography with 5F catheters (11), we decided to explore the feasibility of transradial PTCA and stenting using 6F guiding catheters. We finalized a feasibility study in 100 patients who underwent transradial PTCA (chapter 4.5.1). High successrates and absence of major bleeding complications, made us decide to compare the transradial 6F PTCA technique with 6F PTCA via the femoral or brachial arteries. A randomized trial in 900 patients is currently conducted in our department; the ACCESS- study. We performed an interim analysis at inclusion of 450 patients (chapter 4.5.2).
In the mean time another feasibility study was completed in 100 patients who were selected for transradial coronary stent implantation (chapters 4.6.1, 4.6.2 and 4.6.3).
Since the role of IVUS, guiding coronary stenting, may remain an important issue, we explored the feasibility of ultrasound guided transradial coronary stenting, during stent implantation, with a miniaturized ultrasound transducer (chapter 4.6.4).
Immediate mobilization of the patient after effective hemostasis following a transradial stent implantation, will be associated with considerable cost-savings.
We performed a retrospective comparison of patients who underwent traditional 8F, transfemoral, sheath-protected, stent implantation, derived from the Benestent population, included in our center and transradial stenting. Costs associated with material consumption, diagnosis and treatment of bleeding complications and hospital stay were compared (chapter 4.6.5). To push cost-savings a little further, we conducted a pilot study to the feasibility of coronary stenting on an outpatient basis in a carefully selected group of patients, since an optimal transradial stent result protects the patient against acute stent occlusion and a major bleeding (chapter 4.6.6).

[5] Implantation of non-thrombogenic stents.
Finally Van der Giessen et al. (12) directed attention towards the use of non-thrombogenic heparin-coated Palmaz Schatz coronary stents, with the potential to prevent stent thrombosis, local bleeding complications and to further reduce restenosis. In the pilot-study of the Benestent-II trial, heparin-coated stents were implanted in human coronary arteries. In 4 groups of patients, systemic heparinization was gradually delayed to 36 hours after sheath removal. In the fourth group, no heparin was administered after the procedure and patients were treated with Aspirin and Ticlopidine, instead of antivitamin-K. Results of this pilot-study are given in this thesis (chapter 4.7).

Thus this thesis provides an overview of our 5 years of experience with Palmaz Schatz coro-

nary stenting and of the backgrounds and results of 5 strategies, aimed at an improvement of the clinical outcome of this technique.

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CHAPTER 2.1

TWO MAJOR CLINICAL APPLICATIONS OF PALMAZ SCHATZ CORONARY STENTS

SUBOPTIMAL PTCA RESULTS

FIRST DUTCH EXPERIENCE WITH PALMAZ SCHATZ CORONARY STENTS IN TREATMENT OF ACUTE OCCLUSION AFTER PTCA

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mortality rate was fifty percent. The period of DHCA lasted 7-56 minutes (mean twenty minutes).

There is general agreement on the poor neurological outcome with periods of DHCA exceeding 45 to 60 minutes. Our data supports this view. Above sixty minutes DHCA the incidence of neurological deficits increases sharply. Careful cooling, especially in emergency cases, to limits permitting sufficient time for repair is essential. Three of our patients with a DHCA of less than sixty minutes were cooled inadequately for the duration of the DHCA existing period.

The incidence of multi organ failure was higher in patients with neurological deficits. Thus we can conclude that inadequate cerebral protection coincides with insufficient protection of other organ functions. Multi organ failure has a very high mortality, as shown in many studies. The mortality was 33 percent in our patients with ND and (multi) organ failure. Therefore gradual cooling to safe limits as proposed above is essential. If the expected DHCA time is above 45 minutes the technique of selective cerebral perfusion could be seriously considered.

For successful brain recovery after an ischemic period many other factors play a role. We could show the negative effect of hypotension, severe anemia and hypercapnia. Although hemodilution has favourable effects, especially as a result of decrease in viscosity and better blood flow characteristics, severe hemodilution and anemia interferes with oxygen transport. Together with hypotension severe anemia interferes with a full recovery of the postischemic brain. During the reperfusion period the oxygen requirements increase above basal values.

Hypercapnia induces increase in intracerebral fluid volume. In the reperfusion phase some degree of cerebral edema inevitably occurs. Hypercapnia increases cerebral edema. Mannitol given early in the reperfusion phase, together with prevention of hypercapnia, seems to make sense. Treatment or prevention of hypercapnia can be achieved by removal of carbon dioxide to a greater extent, by means of the heart lung machine, especially before and directly after the period of DHCA.

Although these goals cannot be as easily achieved during surgery as stated here, prevention of hypotension, avoidance of severe hemodilution and hypercapnia seem to be very useful. Treatment of cerebral edema with mannitol after a period of DHCA should be part of the therapy to prevent cerebral damage.

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Neth J Cardiol 1990; 6:190-196

First Dutch experience with Palmaz-Schatz stent in treatment of acute occlusion after PTCA

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Summary

Acute occlusion after PTCA is an emergency situation, often necessitating emergency coronary bypass grafting (CABG). Restoration of blood flow in the occluded vessel after failed PTCA can favourably influence the prognosis. Until recently, only emergency CABG seemed to achieve this goal; implantation of an intravascular prosthesis (stent) however, can also obtain vessel patency, thereby obviating the need for emergency CABG, and possibly for elective CABG as well. In six consecutive patients with acute ischaemia caused by coronary artery dissection during PTCA, a balloon-expandable Palmaz-Schatz stent was used. In one patient the stent could not be implanted, probably because of guiding catheter instability. In the other five patients stent delivery was successful in the absence of cardiac complications during hospitalization. Neither emergency CABG, nor elective CABG, was deemed necessary. Local bleeding complications occurred frequently, due to a rigid antithrombotic regime. In this article the technique of stent implantation is described in a representative patient, followed by the initial results of this small series.

Key words: PTCA, stent

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Introduction

Acute coronary occlusion after percuta-

neous coronary angioplasty (PTCA) occurs in 2 - 12 percent of procedures and may be due to dissection, thrombus, spasm or a combination of these factors.[1] In the first years of the PTCA-era, patients with acute ischaemia after PTCA would have undergone emergency coronary bypass surgery (CABG). However, compared to elective CABG, mortality and morbidity in emergency CABG in these cases is high.[2-5] This is presumably due to deterioration of cardiac performance because of acute ischaemia, or fresh infarction of the myocardium.

Timely restoration of the blood flow to the jeopardized myocardium after failed PTCA should influence the occurrence of ischaemia, infarction, and the outcome of surgery. Ideally it should be able to postpone, or even obviate, the necessity of surgery. One way to restore the blood flow is the use of perfusion catheters.

Another, newer method to achieve this goal is the implantation of an endovascular prosthesis (stent), supporting the dissected arterial wall and safeguarding patency, possibly even in the long run rendering emergency – and elective CABG unnecessary. In this article we describe this treatment in one typical patient, followed by the initial results for six patients with acute occlusion after PTCA.

Material and methods

The Palmaz-Schatz stent is a balloon-expandable articulated stent, consisting of a stainless steel mesh of 0.015 mm filaments, 15 mm in length and measuring 1.5 mm in diameter in collapsed state. The stent is mounted on a LPS dilatation catheter (USCI-Division, CR Bard Inc., Billerica, MA). This catheter is selected for its compliant material (polyvinyl chloride), the balloon length (25 mm) and the presence of a proximal and distal balloon marker, facilitating stent-positioning. Compared to the coronary diameter the balloon catheter must be slightly oversized, to compensate for some inevitable decrease in diameter after stent delivery due to recoil and endothelial covering of the stent.

If occlusion occurs during PTCA the guide wire should be left in place, across the occlusion, in order to safeguard distal access. Over the extended guide wire (USCI) the deflated balloon, without stent, is first advanced towards the occlusion in order to test the ability of the balloon catheter to cross the stenosis.

After this is confirmed the balloon catheter is withdrawn, loaded with the stent and situated in the stenotic area. Then the stent-loaded balloon is inflated up to 10 atmospheres during 10 - 30 seconds thereby compressing the stenosis and delivering the blown-up stent to the dilated arterial wall. Following this the balloon is deflated and withdrawn. Then the result is scrutinized angiographically.

In case of insufficient stenosis reduction the same, or a larger, balloon catheter is advanced into the stented segment and several redilatations can be performed in order to increase the vessel diameter. Further pharmacologic treatment is aimed at the prevention of thrombosis and spasm and consists of the following:

- Rheomacrodex 40 100 ml/hour to a total of one litre, started at the beginning of the procedure.
- Heparin 10,000 IU iv, followed by 2500 IU per hour up to four hours after the procedure and adjusted to maintain APTT (activated partial thrombo-plastin time) between 80 and 100 seconds. The arterial sheath is removed after the heparin had been discontinued for more than three hours. This is followed after three hours by heparin 2500 IU iv and a heparin infusion of 1000 IU per hour until the patient is on full oral anticoagulation.
- Acenocoumarol (Sintrom) during six months: 6 mg the first day, 4 mg the second day, 2 mg the third day followed by a dosage adjusted to maintain a TT (trombotest 'Quick') of approximately fifteen percent.
- Dipyridamole 225 mg/day during six months.
- Aspirin 300 mg/day during six months.
- Diltiazem 180 mg/day.

Immediately before and after stent implantation 200 microgram nitroglycerin is administered intracoronary.

Case history

A 70-year-old man, with severe angina (NYHA III) and a positive stress test, underwent cardiac catheterization in November 1989. This showed a normal left ventricular function in the presence of a proximally occluded right coronary artery, retrogressively filled by collaterals from the left anterior descending (LAD) artery, as well as an eighty percent stenosis in the LAD (fig. 1). It was decided to perform PTCA of the LAD, which was attempted in February 1990. Through a USCI FL 3.5 8F large lumen guiding catheter and over an USCI 0.014 inch very flexible guide wire, a Schneider 3.0 monorail balloon catheter was advanced into the stenosis without problems. After three dilatations (maximally eight atmospheres, 190 seconds), the LAD occluded. Another dilatation restored the flow temporarily, but finally the vessel reoccluded, showing poor antegrade filling in the presence of a dissection (fig. 2). Several intracoronary injections of nitroglycerin were of no avail.

By this time there was constant chest

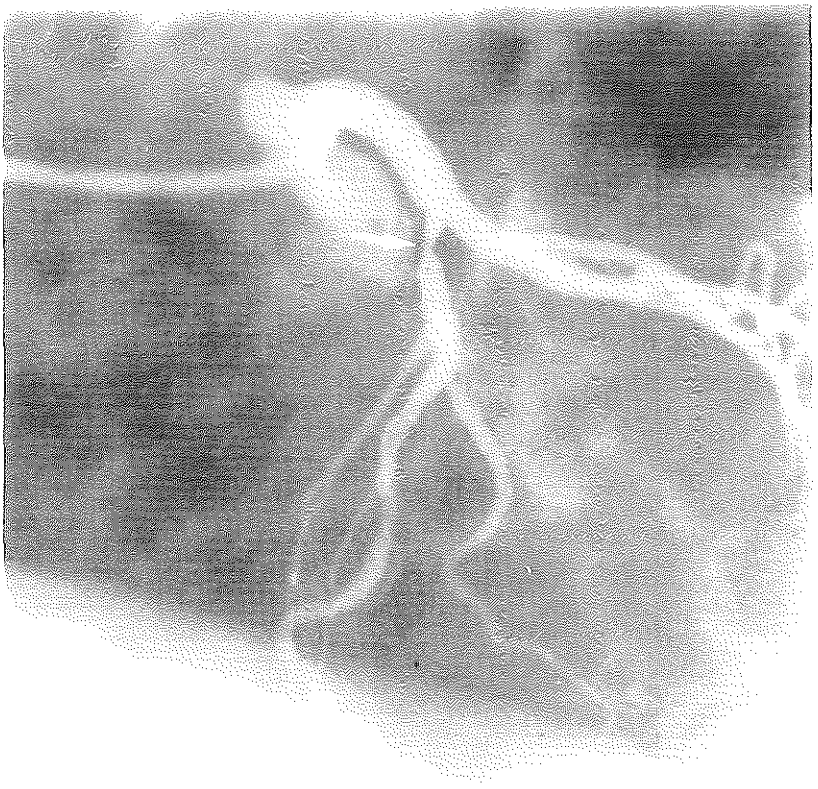

Fig. 1. Before PTCA: left coronary artery in left anterior oblique projection showing a significant proximal LAD-stenosis (arrow).

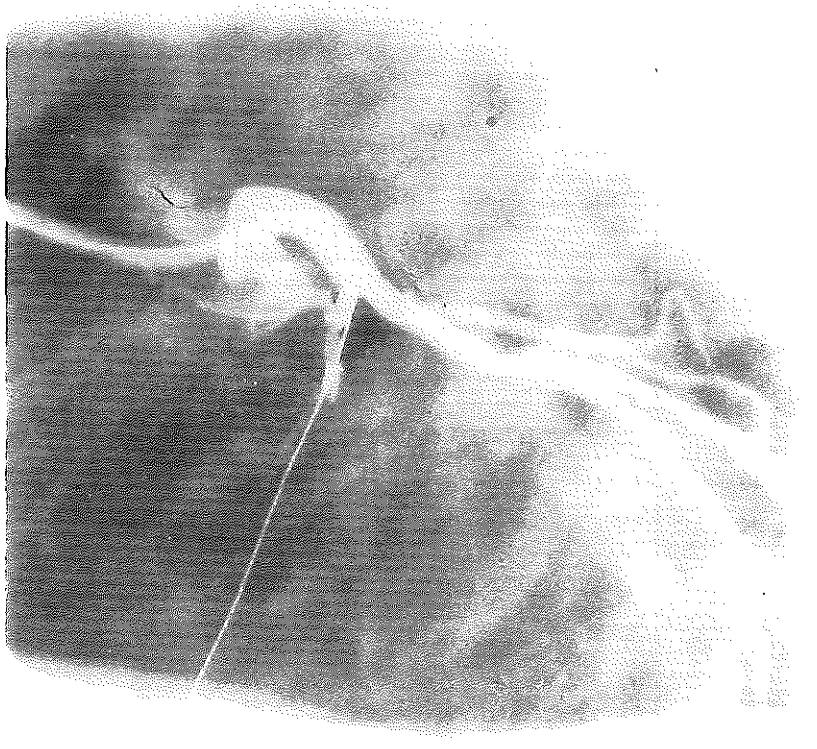

Fig. 2. After PTCA: total occlusion of the LAD.

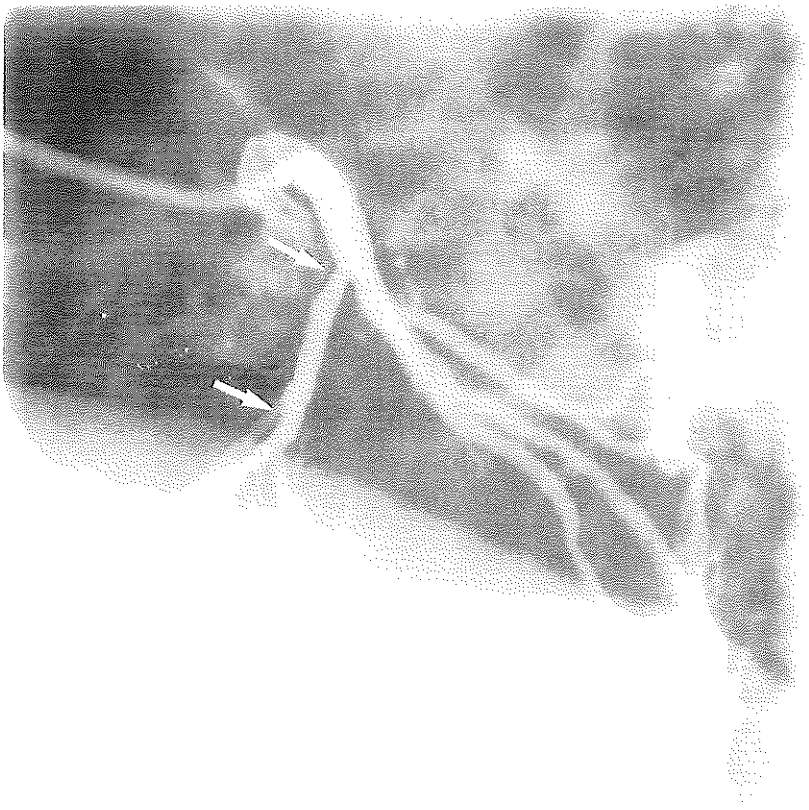

Fig. 3. After stent implantation: patent LAD. Note oversizing of the stented segment (arrows).

pain as well as ST elevations in the precordial leads. It was decided to implant a Palmaz-Schatz stent, which was mounted on an USCI 3.0 LPS balloon catheter. Over the extended guide wire the balloon catheter was advanced towards the lesion without problems. After one dilatation (ten atmospheres during ten seconds) the balloon was deflated and withdrawn over the guide wire.

The pain subsided and the ECG returned to normal. Angiographic control showed no residual stenosis and normal anterograde flow. Diameter in the stent region was about 120 percent of the vessel diameter just proximal and just distal to the stent, due to the fact that the balloon, at ten atmospheres, was oversized, compared to the diameter of the LAD (fig. 3).

The clinical course was complicated by bleeding from the right groin, some hours after removal of the arterial sheath. The bleeding could be stopped by firm and prolonged compression. Blood transfusion was not necessary. There was no electrocardiographic or enzymatic evidence of myocardial infarction. Angiographic control of the LCA, five days later, showed no residual stenosis at the implantation site. The situation was similar to the angiogram immediately after stent implantation.

The patient was free of symptoms at discharge, ten days after stent implantation.

Results

In six patients, two women and four men, with acute ischaemia after PTCA, caused by dissection of the dilated corona-

Table 1

Patient data and results of angiography before and after attempted PTCA

nr.	sex	age	NYHA	vessel	before PTCA		after PTCA	
					%	TIMI	%	TIMI
1	f	72	III	LAD	80	3	90	3
2	m	46	IV	RCA	90	3	90	3
3	m	70	III	LAD	80	3	100	1
4	m	60	III	LAD	80	3	90	3
5	m	63	IV	LAD	80	3	90	3
6	f	69	III	LAD	70	3	80	3

% = minimal internal vessel diameter in stenotic area compared to immediately adjacent normal area of the same vessel (divided by 100); TIMI = see Chesebro e.a.[6]

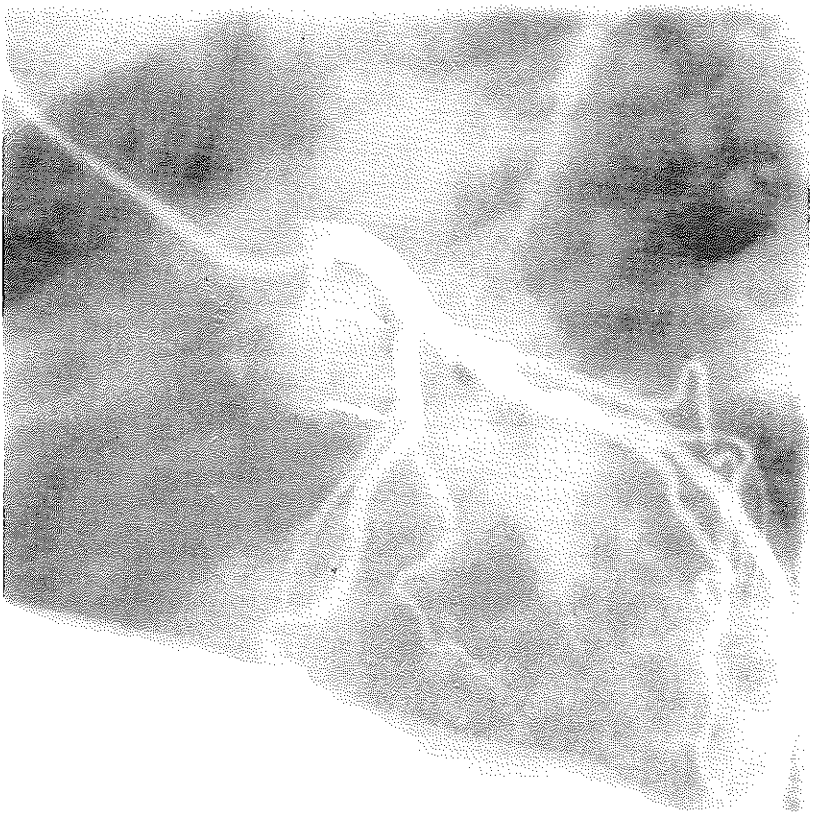

Fig. 4. control after five days: no changes compared to the immediate post-stent left coronary angiogram.

ry artery, a Palmaz-Schatz stent was inserted (table 1). In patient nr. 2 the right coronary artery (RCA) was involved, in all other patients the LAD.

Severity of the stenosis is expressed by percent-diameter stenosis and by the Thrombolysis in Myocardial Infarction (TIMI) grading system[6] before and after the last balloon inflation, prior to stent implantation (table 1).

In patient nr. 5, whose LAD showed a large dissecton after PTCA – although without total occlusion – the stent could not be delivered. The ostium of the left coronary artery could only be reached with an USCI FL5 9F guiding catheter. The naked balloon, though in an unstable position, passed the occlusion without problems, but stent-loaded this proved to be impossible despite several attempts, presumably mainly due to the instability of the guiding catheter in the coronary ostium. The balloon catheter with stent, the guide wire and the guiding catheter were withdrawn and the vessel dit not occlude. The patient then had successful and uncomplicated bypass surgery on the same day.

In our other patients stent delivery was performed within thirty minutes from the start of the initial preparations. No complications were encountered during the procedure, the immediate angiopgraphic results were excellent and no residual stenosis was seen (table 2).

In patient nr. 3, a previously normal first diagonal branch, at the site of the implanted stent, showed only slow anterograde filling after stent placement. This did not result in angina or in myocardial infarction. At recatheterization five days later, the filling of this branch was normal.

Angiographic control was performed four to twelve days after stent implanta-

Table 2

Results of angiopgraphy immediately after stent implantation and at time of repeat angiography

nr.	post-stent	%	TIMI	recath.	%	TIMI
1		0	3	12	0	3
2		0	3	8	0	3
3		0	3	4	0	3
4		0	3	4	0	3
5	stent impl. not possible	90	3	-	-	-
6		0	3	4	0	3

recath. = time of repeat angiography in days after stent implantation; % = see table 1; TIMI = see table 1.

Table 3

Complications of stent implantation

Nr:	
1.	haematoma: puncture site suction
2.	none
3.	haematoma puncture site: conservative treatment
4.	haematoma puncture site: conservative treatment
5.	implantation of stent not possible
6.	haematoma puncture site: conservative treatment

tion (table 2). In all patients the stented segment showed no signs of stenosis, thrombus, dissection or spasm. All patients with a successful stent placement had a stable and uncomplicated clinical course. However, in four patients local bleeding was a major complication; in one patient necessitating percutaneous suction of the haematoma (table 3).

No blood transfusions or surgical interventions were needed. The short follow-up period (2-5 weeks) revealed no stent-related complications. Patient nr. 1 still had anginal complaints due to a significant stenosis in a large first diagonal branch, already present at the time of PTCA. She had a successful PTCA of this branch when re-angiography control was performed twelve days after stent implantation. All other patients were free of angina.

Discussion

Since their introduction by Dotter, a variety of endovascular prostheses are under experimental and clinical evaluation.[7,8] Emergency coronary stent in acute occlusion after PTCA was first described by Sigwart et al.[9] In their series of nine patients implantation of a self-expanding wallstent was technically successful and there were no deaths, myocardial infarctions nor was there need for emergency bypass surgery. Puel et al., however, reported early stent occlusion in twelve of 33 patients treated with the same device.[10] Early acute thrombotic reocclusions have also been described by Bertrand et al. in four of fourteen patients with a wallstent.[11]

The most extensive clinical experience with balloon-expandable stents is obtained with the Palmaz-Schatz stent. Schatz reported on 355 elective Palmaz-Schatz balloon-expandable stent implantations in native coronary arteries in 203 patients.[12] Patients with successful stent delivery (n = 183) were divided in two groups. Forty-five patients were treated with aspirin and dipyridamole, while 138 others were treated additionally with coumarine derivatives during three months. No acute reocclusions occurred in the first 48 hours, but in the ensuing four to ten days closure was noted in seven patients (16 percent) of the first group, but in only five patients (3,6 percent) of the second group.

The process of stent restenosis is very complex.[8] Subacute occlusion is frequently caused by thrombus. Leon e.a. found a higher platelet count and a smaller stent size to be predictors of subacute thrombotic events after placement of the Palmaz-Schatz coronary stent.[13] Other suggestive predictors seem to be the absence of anticoagulants, multiple overlapping stents and presence of thrombus immediately before and after stent placement.[13]

During the short follow-up period in our series no clinical or angiographic signs of restenosis or reocclusion were seen. In four patients significant bleeding occurred on the site of arterial puncture. In one case, local suction of the haematoma was deemed necessary, in all others local pressure sufficed. No blood transfusions were needed. Thus, in our small series, implantation of a stent in an acutely dissecting coronary artery appeared to be feasible, and in most cases helpful, in avoiding emergency bypass surgery. Short term patency was excellent, thereby at least temporarily obviating the need for surgery.

Palmaz-Schatz stents have proved to be useful in postponing emergency CABG in failed PTCA. The capacity of entirely obviating the necessity of coronary surgery of the PTCA-deteriorated vessel needs to be elucidated by long-term results in larger series.

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Induction of circus movement tachycardia by adenosine in Wolff Parkinson White Syndrome

An unexpected observation

Summary

Adenosine is a calcium channel blocker and exerts its effects mainly on the sinus node and the atrioventricular junction. It can be used to terminate circus movement tachycardia originating in the atrioventricular node. It can also be used to unmask latent pre-excitation. We present a case history of a patient with a Wolff Parkinson White syndrome in whom a circus movement tachycardia was unexpectedly initiated by adenosine.

Introduction

Adenosine is the N-glycoside of adenine and is part of DNA, RNA, ATP, cyclic AMP and co-enzyme A. Its cardiovascular effects are direct vasodilatation, stimulation of the baroreflex receptors in the carotid arteries and probably also in the aortic arch. In normal conscious volunteers the haemodynamic effect of adenosine is biphasic; there is a small initial rise in blood pressure followed by tachycardia without significant decrease in blood pressure.

Adenosine blocks the calcium entry in slow response tissue, resulting in sinus bradycardia and slowing of atrioventricular conduction up to second or third degree block. However, sinus bradycardia in particular is counteracted by baroreflex receptor stimulation and the pulmonary stretch receptors.

The very short serum-half-life of less than ten seconds makes adenosine a useful and safe drug for diagnostic and therapeutic purposes. Adenosine has been investigated in sick sinus syndrome. It was also utilized to unmask latent pre-excitation and for the diagnosis of tachycardia of unknown origin. As a therapeutic drug adenosine has been used for terminating circus movement tachycardia using the atrioventricular node. We present an unusual, not previously reported, reaction to adenosine.

Case report

A 21 year old male with the Wolff Parkinson White syndrome was referred for palpitations. He experienced only few, but severely symptomatic, attacks a year. The ECG with pre-excitation is shown in fig. 1. Physical examination, echocardiography and chest X-ray were performed and showed no cardiac abnormalities.

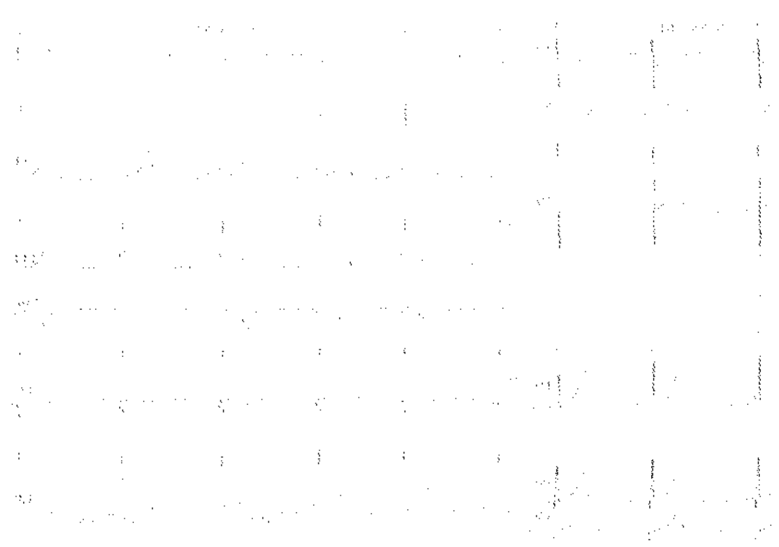

Fig. 1. The 12-lead ECG [illegible]

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CHAPTER 2.2

TWO MAJOR CLINICAL APPLICATIONS OF PALMAZ SCHATZ CORONARY STENTS

SUBOPTIMAL PTCA RESULTS

EMERGENCY CORONARY STENTING WITH THE PALMAZ SCHATZ STENT FOR FAILED TRANSLUMINAL CORONARY ANGIOPLASTY: RESULTS OF A LEARNING PHASE

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Emergency coronary stenting with the Palmaz-Schatz stent for failed transluminal coronary angioplasty: Results of a learning phase

This study describes initial results of Palmaz-Schatz stent implantation in our department to restore and maintain vessel patency in 52 patients with obstructive dissection, defined as an intraluminal filling defect with coronary flow impairment after percutaneous transluminal coronary angioplasty (PTCA). The majority of patients (62%) underwent PTCA for unstable angina ($n = 28$), defined as angina at rest with documented ST segment changes resistant to nitrates, or acute myocardial infarction ($n = 4$). In six patients (11%) the stent could not be delivered. Seven of the remaining 46 patients (15%) had coronary artery bypass surgery performed because of increased risk for subacute stent occlusion, residual thrombosis, residual obstruction near the stent, coronary artery diameter less than 3.0 mm, or multiple and overlapping stents. One patient (3%) died in hospital from intracranial bleeding. Nine patients (23%) had subacute stent occlusion, retrospectively unpredictable in four patients. Nine of 29 patients (29%) with an uncomplicated clinical course after stenting had angiographic restenosis at a mean follow-up of 6.0 ± 1.4 months (range 12 days to 8.3 months). Two patients (7%) died 3 months after successful stenting: one patient because of stent thrombosis after stopping warfarin before an abdominal operation and one patient after acute vascular surgery for late traumatic groin bleeding. Of the 39 medically treated patients with a stent, three (8%) had major bleeding complications. It is concluded that stent implantation is feasible in most patients with obstructive dissection after PTCA. After successful stent delivery, coronary flow is temporarily restored. However, during this early experience with emergency stenting, it was shown that non-surgical treatment of these patients resulted in substantial subacute stent occlusion rates. Accordingly, stabilized patients should be considered as a high-risk population for subacute stent thrombosis, needing careful monitoring of anticoagulant treatment and ambulation. Semielective bypass surgery after emergency stenting may be the treatment of choice. With a combination of an optimal angiographic result and an optimal clinical infrastructure and patient management, a more conservative treatment after emergency stent implantation may be advocated. (Am Heart J 1993;126:23-31.)

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The early National Heart, Lung, and Blood Institute (NHLBI) percutaneous transluminal coronary angioplasty (PTCA) registry (1979 to 1983) reported on the PTCA experience in the United States. With a primary success rate of 67%, myocardial infarctions occurred in 5.5% of patients, urgent bypass surgery was necessary in 6.6%, and death occurred in 0.9%.[1] In the later registry (1985 to 1986), the success rate was 88%; 4.3% of the patients suffered from nonfatal myocardial infarction, 3.4% needed emergency bypass surgery, and the death rate was 1.0%.[2] Despite advances in technology in PTCA equipment and despite increased operator skill, PTCA still carries the risk of acute postprocedural coronary artery occlusion, which occurs in 3% to 7.3% of patients.[3-6] Several mechanisms contribute alone or in combination to abrupt closure: disruption of the plaque with intimal dissection, subintimal hematoma, coronary thrombosis, and spasm. Emergency bypass surgery after failed PTCA has considerable risk for perioper-

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ative myocardial infarction, with mortality rates of 3% to 18% of patients.[6-10] Ongoing ischemia especially contributes to perioperative mortality and morbidity.[9] Therefore stabilization of the patient with acute occlusion after PTCA may improve the outcome of surgery. Stabilization of a number of patients can be obtained with repeat PTCA if the procedure can be accomplished immediately and the lesion can be crossed. Coexistent intracoronary thrombosis may be treated with intracoronary thrombolytic agents. Hemodynamic support by intraaortic balloon pumping may be mandatory.[11]

After provisional recanalization, different strategies have been described to maintain vessel patency; balloon inflations of long duration[12] or newer treatment modalities such as laser balloons,[13] various atherectomy devices,[14] and intracoronary endovascular supporting prostheses or stents[15-19] have been mentioned as "bail-out" devices. Implantation of intracoronary stents by skilled operators and in experienced centers is a promising technique to seal off intimal flaps after PTCA, to improve vessel geometry and flow, and to prevent elastic recoil. In the present report our experience during a learning phase is described with the Palmaz-Schatz stent, used in the treatment of obstructive dissection after PTCA.

METHODS

Percutaneous transluminal coronary angioplasty. The x-ray imaging equipment used was the Philips Poly Diagnost C1 (Philips Medical Systems International BV, DA Best, The Netherlands), powered by an Optimus M 200 generator (Philips Medical Systems International BV) and equipped with a Digital Cardiac Imaging system (DCI). This system gives on-line video digitized images for optimal angiographic assessment of coronary artery anatomy. PTCA was performed in all patients by means of a femoral approach, with the use of an over-the-wire technique. In the persistence of a >50% stenosis and coronary flow impairment, caused by intimal dissection despite application of intracoronary nitroglycerin and prolonged dilatations with conventional or perfusion catheters, it was decided to implant a Palmaz-Schatz stent. Contraindications for coronary stenting were considered to be: excessive tortuosity of the segment proximal to the occlusion; vessel diameter less than 3.0 mm; evident intracoronary thrombus; contraindications for anticoagulation; and diffusely diseased coronary arteries with multiple significant lesions.

Stent implantation. The Palmaz-Schatz articulated stent consists of a balloon-expandable stainless steel meshwork, 15 mm in unexpanded length and 1.6 mm in diameter in the collapsed state. The stent has two 7 mm segments connected by a 1 mm bridging strut. The stent filaments are 0.015 mm in thickness. The stent is crimped onto a standard PTCA balloon catheter. This stent-loaded balloon catheter is advanced over the guide wire to the obstructing lesion. After careful positioning, the stent is delivered, followed by deflation and withdrawal of the PTCA catheter and then by control angiography. Compared with the coronary artery diameter, the stented segment is slightly overdilated by repeat dilatations with higher inflation pressures or with a larger balloon to compensate for decrease of the stent diameter after delivery. Stenting was performed by four operators having different levels of experience with this technique, with one operator coaching the others initially.

Medical treatment. Immediately before and after stent deployment 200 μg of nitroglycerin was given via the intracoronary route. Further pharmacologic treatment was aimed at the prevention of thrombosis and spasm and consisted of the following. (1) Dextran 40, administered in doses of 100 cm^3/hour to a total of 1 liter, started from the moment the decision was made to implant a stent. (2) Heparin, 10,000 IU, was administered through the femoral artery sheath after its insertion, followed by 5,000 IU for each hour the procedure lasted. A second 10,000 IU bolus of heparin was given after stent implantation. A heparin infusion was continued for 24 hours and was adjusted to maintain activated partial thromboplastin time (APTT) between 80 and 100 seconds. The arterial sheath was removed after the heparin had been discontinued for more than 3 hours at an APTT less than twice normal. This was followed after 1 hour by a bolus of 5,000 IU of intravenous heparin and a heparin infusion titrated according to the APTT, measured at 8-hour intervals.

(3) Acenocoumarol (Sintrom, Ciba-Geigy BV, Arnhem, The Netherlands) was given for 3 months: 6 mg the first day, 4 mg the second day, 2 mg the third day, followed by a dosage adjusted to maintain a TT (thrombotest "QUICK", Pharmachemie, Haarlem, The Netherlands) of 5% to 10%. Heparin was continued for a minimum of 5 days and was stopped when the patient had a TT in the therapeutic range. (4) Dipyridamole was given in a dose of 225 mg/day for 6 months. (5) Acetylsalicylic acid, 300 mg/day, was given for 6 months. (6) Diltiazem, 180 mg/day, was given for 3 months. This protocol was readjusted several times during the study according to new experience and insights.

Postprocedural care. After the procedure, each patient was taken to the coronary care unit or to the cardiac ward, with the arterial sheath left in situ. Initially, the sheath was removed after at least 24 hours of heparinization, with heparin temporarily being discontinued to obtain adequate local hemostasis. In a later phase of the study, heparin was discontinued immediately after the procedure. When the APTT was less than twice normal, the sheath was withdrawn, followed by heparinization after 1 hour. After sheath removal the groin was compressed manually, until hemostasis was achieved, followed by a compression bandage for 8 hours and a 24-hour immobilization period.

Data collection. Clinical, procedural, and postprocedural data were prospectively collected in a data base file. Cineangiograms were judged for diameter stenosis using electronic calipers, Thrombolysis In Myocardial Infarction (TIMI) grade flow, and for the presence of thrombus and

dissection before and after PTCA and after stent implantation. Values are expressed as mean ± standard deviation.

Definitions. *Failed PTCA* = unresolved or recurrent stenosis ≥ 50% during or immediately after the procedure, caused by an obstructive intimal dissection. *Obstructive intimal dissections* = intraluminal linear filling defect or a luminal filling defect with irregular borders, causing coronary flow impairment. *Intracoronary thrombus* = discrete intraluminal filling defect surrounded by contrast material, visible in two orthogonal projections. *Unstable angina* = recurrent episodes of chest pain with documented ST segment changes, resistant to nitrates. *Acute myocardial infarction* = two or more of the following criteria: (1) development of new Q waves; (2) a total creatine kinase (myocardial band) elevation of more than twice the normal upper value; and (3) prolonged chest pain. *Stent occlusion* = angiographically proven stent occlusion with loss of 1 grade of TIMI flow (acute: within 24 hours after delivery; subacute: beyond 24 hours after delivery during the initial hospitalization; late: after discharge). *Late restenosis* = diameter stenosis ≥ 50% more than 1 month after stent implantation. *Prophylactic coronary bypass surgery* = bypass surgery involving the previously stented vessel, with the vessel being patent and the patient in a nonischemic state. *Inadequate (under)anticoagulation* = more than two consecutive APTT values under 80 seconds with TT values over 10%. *Major bleeding* = bleeding leading to death, needing surgery or requiring blood transfusion. *Minor bleeding* = bleeding without need for surgery or blood transfusion.

RESULTS

From January 1990 to June 1991, PTCA was performed on 961 patients at our institution. Seventy-five patients received an intracoronary Palmaz-Schatz stent for varying indications (Fig. 1). In 52 patients stent implantation was attempted for failed PTCA (5.4% of PTCA; 69% of stent implantations) (Fig. 2.). Clinical baseline characteristics are summarized in Table I. Table II provides more detailed patient data. Patient numbers in the text are referenced to Table II. Of 29 conservatively treated patients having successful stent implantation and an uncomplicated hospitalization phase, 22 patients were angiographically examined 6 months after discharge (mean 6.0 ± 1.4; range 12 days to 8.3 months).

Hospital course

Failed stent delivery. A Palmaz-Schatz stent could be successfully delivered in 46 patients. In five patients (9.6%) inability to deliver the stent was caused by inability to reach or cross the stenosis. One female patient (No. 22), had a total left anterior descending (LAD) artery occlusion after PTCA. After the guide wire had recrossed the occlusion, stent delivery was attempted. After stent implantation no distal flow was visible from the stent. An effort was made to restore flow by multiple dilatations before subintimal delivery of the stent, advanced over a subintimally positioned guide wire, was considered. Because the distal LAD was damaged by these subintimal dilatations, the vessel was considered unsuitable for bypass grafting. She had minor chest pain, no electrocardiographic (ECG) changes, and a maximal creatine kinase (myocardial band) of 25 IU/L. Two patients (Nos. 12 and 41) were successfully managed with prolonged inflations with an oversized reperfusion catheter. One patient (No. 43) unsuitable for coronary bypass surgery with a residual significant stenosis, was treated medically, and two patients (Nos. 16 and 29) had uncomplicated elective coronary bypass surgery.

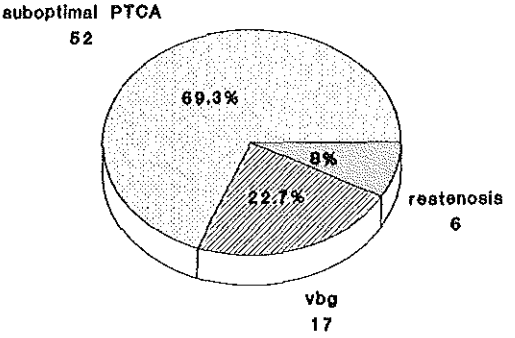

Fig. 1. Indications for stent implantation from January 1990 to June 1991 in 75 patients.

Bridge to coronary artery bypass surgery. Of the remaining 46 patients (88% of total attempts) with successful stent implantation, seven patients (15%) were sent for coronary bypass surgery in a stable condition and without signs of ischemia. In four patients (Nos. 8, 20, 46, and 52) surgery was indicated because of a persisting intraluminal filling defect caused by thrombus or dissection at the stent implantation site. Two patients (Nos. 21 and 38) had bypass surgery because of multiple and overlapping stents, which was considered a high risk for subacute thrombosis. One patient (No. 36) was operated upon because of an allergic reaction to aspirin.

Stent occlusion. Acute stent occlusion was not encountered in this group of 39 medically treated patients after successful stent delivery. Nine patients (23%) had subacute stent occlusion. Six patients (Nos. 7, 9, 17, 34, 50, and 51) were operated upon directly after successful recanalization by means of repeat PTCA of the occluded stent. Two patients had

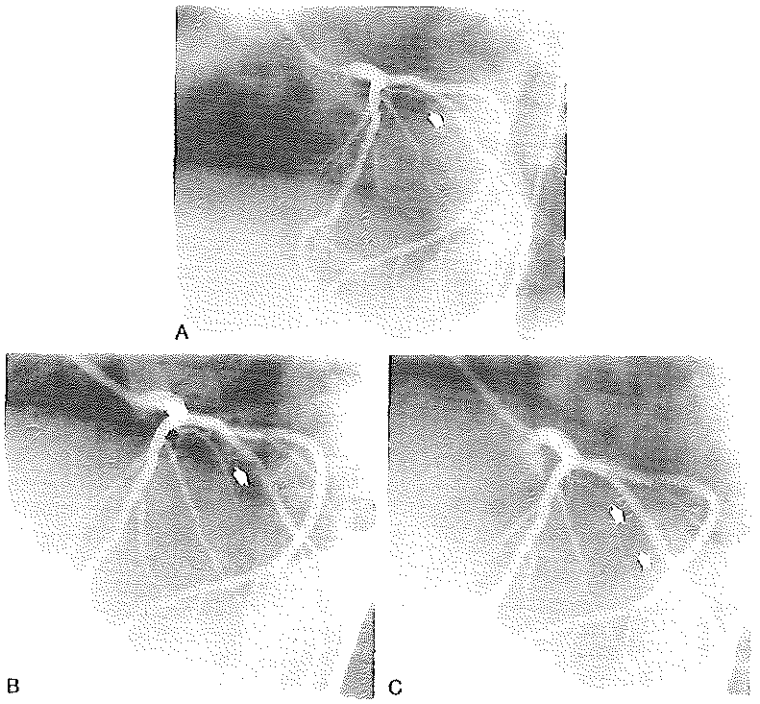

Fig. 2. **A,** Vessel pre-PTCA. Significant stenosis in anterolateral branch *(arrow).* **B,** After PTCA. Dissection after repeated dilatations *(arrow).* **C,** After stent implantation. Optimal angiographic result *(arrows).*

a successful repeat PTCA, but were considered unsuitable for coronary bypass surgery because of malignant disease (No. 13) or previous infarction in the stent-related myocardial region (No. 27). Recrossing an occluded LAD stent failed in one patient (No. 33), resulting in an extension of a previous anterior infarction. Retrospectively, two patients had inadequate anticoagulation (Nos. 13 and 33), three (Nos. 27, 34, and 51) had a persisting obstruction near the stent, and one patient (No. 27) had both. In four patients (Nos. 7, 9, 17, and 50) no detectable cause for stent thrombosis was found.

Bleeding complications. Minor bleeding complications (21%) were puncture site-related (75%) in the majority of cases. Major bleeding complications were seen in three (8%) patients, one (No. 45) with vaginal bleeding requiring blood transfusions and one (No. 21) with a false aneurysm in both groins requiring surgery. The third patient (No. 14), whose condition was inoperable because of severe left ventricular dysfunction, left the catheterization laboratory with residual thrombus in the stent that was treated with intracoronary and intravenous streptokinase. One day later, this patient had fatal intracranial bleeding.

Follow-up

Late restenosis. Of the 29 patients without cardiac complications after successful stent implantation at discharge, 22 (76%) had control angiography 6 months (mean 6.0 ± 1.4; range 12 days to 8.3 months) after stent implantation. One patient (No. 10) was readmitted 12 days after stent implantation in a right coronary artery (RCA), with an extension of a previous inferior myocardial infarction. Recatheterization revealed total stent occlusion, successfully recanalized by repeat PTCA. His TT was 4% on the day of stent occlusion. Eight patients (28%) had significant restenosis. Four patients (Nos. 19, 25, 37, and 39) had elective coronary artery bypass grafting (CABG). One patient (No. 42) had successful PTCA; however, his condition was complicated by restenosis within 2 months. This patient underwent uncomplicated

CABG electively. Two patients (Nos. 26 and 31) had successful PTCA 6 months after stent implantation, and one patient (No. 48) was treated conservatively because of absence of angina pectoris.

Late mortality. Two patients (Nos. 10 and 45) died 3 months after stent implantation (7%). One patient (No. 10) with traumatic bleeding in the groin after alcohol abuse was admitted in hypovolemic shock. After surgical repair, the clinical course was complicated by pneumonia and a fatal cerebrovascular accident. The other patient (No. 45) died following an abdominal operation 3 months after successful stent implantation in the LAD. Warfarin was stopped preoperatively. Postoperatively, this patient died in cardiogenic shock caused by an evolving anterior myocardial infarction. At postmortem examination, the stent was found restenosed and a fresh thrombus was visible within the stent.

DISCUSSION

Bredlau et al.[20] reported on 3500 patients undergoing elective PTCA. Major ischemic complications were seen in 12%: 10.4% showed angiographic signs of intimal dissection, compared with 1.6% of patients without evidence of dissection. By implantation of a coronary stent the intimal dissection can be sealed off, offering a solution for abrupt closure after PTCA. If it has been well delivered, a stent maintains vessel patency and ischemia is alleviated, obviating the need for high-risk emergency bypass surgery in a patient with acute myocardial ischemia. However, patients with acute or impending ischemia after suboptimal PTCA also form a difficult population for emergency coronary stenting. Decisions have to be made ad hoc because of the emergency nature of the intervention. Patients with complex coronary anatomy and pathology may be subjected to this technique in the hope of restoring flow for at least some time. Stent implantation itself has to be performed rapidly in a patient without proper medical preparation.

Emergency coronary stenting is reported by Roubin et al.,[15] using the Gianturco-Roubin stent (Cook Inc., Bloomington, Ind.); by Sigwart et al.[16] and De Feyter et al.[17] with the Medinvent self-expanding wall stent (Medinvent Inc., Englewood, N.J.) by Vrolix et al.,[18] using the balloon-expandable Medtronic Wiktor coronary stent (Medtronic, Inc., Minneapolis, Minn.); and by Schatz et al.[19] with the Johnson & Johnson balloon-expandable Palmaz-Schatz stent (Johnson & Johnson Interventional Systems, Warren, N.J.). The present study reports on the early experience in our department with the Palmaz-Schatz coronary stent in the treatment of failed PTCA. Several clinical and technical problems were encountered during this learning phase, and several solutions were introduced over the course of time.

Table I. Baseline characteristics of patient population

	No.	*Percent*
No. of patients	52	
Male gender	42	81%
Age	27-74 yr	(58 ± 10.5)
Presentation		
NYHA I	3	6%
NYHA II	0	0%
NYHA III	17	32%
NYHA IV	28	54%
Acute MI	4	8%
Vessel of stented coronary artery		
LAD	32	62%
LCX	4	8%
AL	2	4%
RCA	14	26%
Type of coronary lesion		
Type A	17	33%
Type B	13	25%
Type C	22	42%
Single-vessel disease	32	62%
Two-vessel disease	13	25%
Three-vessel disease	7	13%
Prior myocardial infarction	30	58%
Prior bypass surgery	1	2%
Hypertension	11	21%
Diabetes mellitus	2	4%
Cholesterol ≥6.5 mmol/L	12	23%
Current cigarette smoker	19	37%
Family coronary artery disease	9	17%

AL, Anterolateral branch; *Acute MI*, acute myocardial infarction; *LAD*, left anterior descending artery; *LCX*, left circumflex artery; *NYHA*, New York Heart Association; *RCA*, right coronary artery.

In the present study, the stent could not be delivered in six patients (11%). Schatz et al.[21] analyzed failed delivery in their report on the initial results of clinical experience in a multicenter study with the Palmaz-Schatz coronary stent. Successful delivery with the articulated stent was more likely in the RCA and LAD coronary arteries compared with the circumflex artery, in proximal versus distal lesions, and when there was no evidence of dissection after PTCA. The Stent Delivery System (SDS) (Johnson and Johnson Interventional Systems) was developed to improve the safety and success rates of stent implantation, with less chance of proximal deployment and stent embolization.[22] This system consists of a factory preassembled unit, with an articulated stent crimped onto a balloon catheter of varying diameter between two radioopaque markers, covered by a 5F protecting sheath. In our initial experience, however, the SDS was not available or in common use in emergency situations. This is partially explained by

Table II. Patient population: Clinical characteristics and outcome

Patient No.	*Sex*	*Age*	*PTCA ind.*	*Vessel*	*Success*	*Event-free*	*Bleeding*	*SAC*	*rePTCA*	*CABG*	*AMI*	*Restenosis*	*Death*
1	M	46	UAP	LAD	Yes	No	No	No	No	Yes	No	No	No
2	M	65	SAP I	LCX	Yes	Yes	No	No	No	No	No	No	No
3	M	72	SAP I	RCA	Yes	Yes	No	No	No	No	No	No	No
4	M	54	UAP	AL	Yes	No	Minor	No	No	No	No	No	No
5	M	69	AMI	LAD	Yes	Yes	No	No	No	No	No	No	No
6	M	65	SAP III	RCA	Yes	No	Minor	No	No	No	No	No	No
7	M	66	SAP III	RCA	Yes	No	No	Yes	Yes	Yes	Yes	No	No
8	M	72	SAP III	LAD	Yes	No	No	No	No	Yes	No	No	No
9	F	69	UAP	RCA	Yes	No	No	Yes	Yes	Yes	No	No	No
10	M	68	AMI	RCA	Yes	No	Minor	Yes	Yes	No	Yes	No	Yes
11	M	43	AMI	RCA	Yes	Yes	No	No	No	No	No	No	No
12	M	48	UAP	RCA	No	Yes	No	—	No	No	No	—	No
13	F	64	UAP	LAD	Yes	No	No	Yes	Yes	No	Yes	No	No
14	M	69	SAP I	LAD	Yes	No	Major	No	No	No	No	No	Yes
15	M	72	UAP	LAD	Yes	No	Minor	No	No	No	No	No	No
16	M	50	SAP III	LAD	No	No	No	—	No	Yes	No	—	No
17	M	62	SAP III	LAD	Yes	No	No	Yes	Yes	Yes	No	No	No
18	M	46	UAP	RCA	Yes	Yes	No	No	No	No	No	No	No
19	F	70	UAP	LAD	Yes	No	No	No	No	Yes	No	Yes	No
20	M	37	SAP III	LCX	Yes	No	No	No	No	Yes	No	No	No
21	F	64	UAP	LAD	Yes	No	Major	No	No	Yes	No	No	No
22	F	61	UAP	LAD	No	No	No	—	No	No	Yes	—	No
23	M	68	SAP III	LAD	Yes	Yes	No	No	No	No	No	No	No
24	M	44	SAP III	OM	Yes	Yes	No	No	No	No	No	No	No
25	M	59	UAP	LAD	Yes	No	No	No	No	Yes	No	Yes	No
26	F	52	SAP III	LAD	Yes	No	Minor	No	Yes	No	No	Yes	No
27	M	69	UAP	LAD	Yes	No	No	Yes	Yes	No	Yes	No	No
28	M	55	UAP	LAD	Yes	Yes	No	No	No	No	No	No	No
29	M	63	UAP	LAD	No	No	No	—	No	Yes	No	—	No
30	M	56	SAP III	RCA	Yes	Yes	No	No	No	No	No	No	No
31	M	72	UAP	LAD	Yes	Yes	No	No	Yes	No	No	Yes	No
32	M	27	UAP	RCA	Yes	No	Minor	No	No	No	No	No	No
33	F	61	AMI	LAD	Yes	No	No	Yes	Yes	No	Yes	No	No
34	M	54	SAP III	RCA	Yes	No	No	Yes	Yes	Yes	No	No	No
35	F	72	SAP III	RCA	Yes	No	Minor	No	No	No	No	No	No
36	M	45	UAP	LAD	Yes	Yes	No	No	No	Yes	No	No	No
37	M	50	SAP III	LAD	Yes	No	No	No	No	Yes	No	Yes	No
38	M	57	UAP	RCA	Yes	No	No	No	No	Yes	No	—	No
39	M	70	SAP III	LAD	Yes	No	Minor	No	No	Yes	No	Yes	No
40	M	54	UAP	LAD	Yes	Yes	No	No	No	No	No	No	No
41	M	55	UAP	LAD	No	Yes	No	—	No	No	No	—	No
42	M	46	UAP	LAD	Yes	No	No	No	Yes	Yes	No	Yes	No
43	M	52	SAP III	LCX	No	Yes	No	—	No	No	—	—	No
44	M	55	UAP	LAD	Yes	No	Minor	No	No	No	No	No	No
45	F	69	UAP	LAD	Yes	No	Major	No	No	No	Yes	Yes	Yes
46	M	53	UAP	LAD	Yes	No	No	No	No	Yes	No	No	No
47	F	74	UAP	LAD	Yes	Yes	No	No	No	No	No	No	No
48	M	52	SAP III	LAD	Yes	No	No	No	No	No	No	Yes	No
49	M	43	UAP	RCA	Yes	No	No	No	No	No	No	No	No
50	M	55	UAP	LAD	Yes	No	No	Yes	Yes	Yes	No	No	No
51	M	58	UAP	LAD	Yes	No	No	Yes	Yes	Yes	No	No	No
52	M	64	SAP III	AL	Yes	No	No	—	No	Yes	No	—	No

AMI, Acute myocardial infarction; *CABG*, coronary artery bypass grafting; *F*, female; *M*, male; *OM*, obtuse marginal branch; *PTCA ind.*, PTCA indication; *SAC*, subacute stent closure; *SAP*, stable angina pectoris; *UAP*, unstable angina pectoris; other abbreviations as in Table I.

a reluctance to change the guiding catheter for one with a larger inner lumen diameter, necessary to ensure passage and adequate positioning of the SDS. This exchange procedure may be complicated by loss of distal access of a damaged coronary artery. Starting PTCA with a large lumen guiding catheter (at least 0.82 inch inner luminal diameter) may have prevented this problem.

All patients with successful stent implantation had a patent vessel, with relief of myocardial ischemia. Thus the immediate success rate was high (88%). However, 21 patients (45%) needed bypass surgery either because of an anticipated high risk for subacute stent occlusion (15%) or for subacute stent thrombosis or late restenosis (30%). Only 0.6% of anticoagulated patients suffered from subacute stent occlusion in the multicenter study of elective cases reported by Schatz et al.[21] This complication rate compares favorably with the results achieved with the self-expanding wall stent reported by Sigwart et al.,[23] Puel et al.,[24] and Serruys et al.[25] The results in favor of the Palmaz-Schatz stent may be a result of the high concentration of metal in the self-expanding stent, making the stent more thrombogenic, as the open area of the expanded Palmaz-Schatz stent is 90%. The subacute stent thrombosis rates after suboptimal angioplasty, as reported by Schatz et al.[26] (5.3%), Kimura et al.[27] (9.3%), Haude et al.[28] (12%), and Fajadet et al.[29] (29.4%), are substantially higher compared with this complication rate in the electively stented patient group receiving warfarin (4.5%), according to the multicenter experience.[21] The subacute occlusion rate in our group of medically treated patients with emergency implanted stents is also high (23%).

Several factors may contribute to the difference in subacute occlusion rates in electively stented coronary arteries. Fischman et al.[30] reported on angiographic predictors of subacute stent thrombosis in a group of 726 patients with a Palmaz-Schatz coronary stent. Intraprocedural thrombus and persistent dissection as well as suboptimal results after PTCA were associated with an increased risk for subacute thrombosis. Thrombus formation just before, during, or after stent implantation may have played an important role in our patient population, since a majority of our patients underwent PTCA for unstable ischemic heart disease, thus having a higher tendency of intracoronary thrombosis than those having elective PTCA for stable angina pectoris.[10,31]

If active thrombosis is suspected, stent implantation had better be avoided, prolonged local administration of thrombolytic agents being preferable. If this treatment fails to restore vessel patency, a stent may be implanted as a bridge to immediate coronary artery bypass surgery. A second possible cause may be suboptimal medical preparation for emergency stenting, the patients not having received anticoagulants and aspirin and lacking premedication with dextran before stent implantation. Although the role of dextran in the prevention of stent thrombosis is a matter of debate,[32] we now administer dextran to patients at the start of an elective PTCA. If a patient had not used aspirin, its intravenous form (Aspegic, Searle Farmaca, Weesp, The Netherlands) could be administered at the time of stent implantation.

Finally, the treatment of dissections with multiple dilatations of oversized balloon catheters may increasingly damage the vessel, creating a larger thrombogenic surface and thus enhancing the chance of subacute closure. Dissection extension beyond the stent may contribute to inflow or outflow obstruction, with increased risk for subacute occlusion.[26] If the PTCA is complicated by an occlusive dissection, implantation of a stent should not be postponed to the very last moment. Extension of the dissection beyond the stent must be treated with one or more, not overlapping, stents.

Monitoring of APTT and TT may be insufficient to prevent subacute stent thrombosis even after training of medical, nursing, and laboratory staff. Erbel et al.[33] reported on the determination of F1 + 2 prothrombin fragments for monitoring of heparin (therapeutic level <0.5 nmol/L) and of factor II for monitoring warfarin treatment (therapeutic level <42%). In a group of 25 patients, no subacute thrombosis occurred, compared with 16.9% in a historical group of 54 patients without monitoring of these markers. Introduction of monitoring of these parameters may improve the outcome of patients with emergency implanted stents. In the multicenter study of Schatz et al.,[21] 8.5% of patients receiving anticoagulation had bleeding complications. In our group, 8% of patients developed major bleeding complications. The majority of minor bleeding complications (21%) were puncture site-related. This may be related to an overshoot of heparin after stent implantation and to sheath removal under some degree of anticoagulation.

New vascular devices (VasoSeal, Datascope Corp., Montvale, N.J.) containing collagen for supraarterial application to enhance hemostasis, even under full heparinization, show promise in reducing this complication. In an international registry reported by Ernst et al.,[34] 100 fully anticoagulated patients had an 8F sheath removed and 180 mg of bovine collagen applied through an over-the-wire vascular hemostasis device. Hemostasis was obtained in 94% within 5 minutes, without device-related complications. Another advantage of these devices may be the possibility of continuing heparin infusion immediately after stent implantation, obviating the necessity to withdraw heparin before sheath removal, with a possible reduction of subacute stent closures.

In conclusion, implantation of a Palmaz-Schatz coronary stent on an emergency basis after suboptimal PTCA proved to be feasible, with high primary success rates. However, during this early experience, nonsurgical treatment of patients with successfully

implanted stents resulted in substantial subacute stent occlusion and bleeding complication rates. Therefore patients with emergency implanted stents should be considered a high-risk population for subacute stent occlusion and should be monitored carefully during aggressive anticoagulant treatment and careful ambulation. Keeping in mind the excellent results of CABG in a patient without ongoing cardiac ischemia, patients should be referred for CABG within 24 hours after emergency stent implantation if additional risks for stent occlusion are present. This applies especially for less experienced centers. With improving patient selection, medical preparation, stent implantation techniques, and hemostatic management, in combination with an optimal clinical infrastructure, a more conservative treatment after emergency stent implantation may be advocated.

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CHAPTER 2.3

TWO MAJOR CLINICAL APPLICATIONS OF PALMAZ SCHATZ CORONARY STENTS

PRIMARY STENT IMPLANTATION FOR REDUCTION OF RESTENOSIS

A COMPARISON OF BALLOON EXPANDABLE STENT IMPLANTATION WITH BALLOON ANGIOPLASTY IN PATIENTS WITH CORONARY ARTERY DISEASE

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A COMPARISON OF BALLOON-EXPANDABLE–STENT IMPLANTATION WITH BALLOON ANGIOPLASTY IN PATIENTS WITH CORONARY ARTERY DISEASE

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Abstract *Background.* Balloon-expandable coronary-artery stents were developed to prevent coronary restenosis after coronary angioplasty. These devices hold coronary vessels open at sites that have been dilated. However, it is unknown whether stenting improves long-term angiographic and clinical outcomes as compared with standard balloon angioplasty.

Methods. A total of 520 patients with stable angina and a single coronary-artery lesion were randomly assigned to either stent implantation (262 patients) or standard balloon angioplasty (258 patients). The primary clinical end points were death, the occurrence of a cerebrovascular accident, myocardial infarction, the need for coronary-artery bypass surgery, or a second percutaneous intervention involving the previously treated lesion, either at the time of the initial procedure or during the subsequent seven months. The primary angiographic end point was the minimal luminal diameter at follow-up, as determined by quantitative coronary angiography.

Results. After exclusions, 52 patients in the stent group (20 percent) and 76 patients in the angioplasty group (30 percent) reached a primary clinical end point (relative risk, 0.68; 95 percent confidence interval, 0.50 to 0.92; P = 0.02). The difference in clinical-event rates was explained mainly by a reduced need for a second coronary angioplasty in the stent group (relative risk, 0.58; 95 percent confidence interval, 0.40 to 0.85; P = 0.005). The mean (±SD) minimal luminal diameters immediately after the procedure were 2.48±0.39 mm in the stent group and 2.05±0.33 mm in the angioplasty group; at follow-up, the diameters were 1.82±0.64 mm in the stent group and 1.73±0.55 mm in the angioplasty group (P = 0.09), which correspond to rates of restenosis (diameter of stenosis, ≥50 percent) of 22 and 32 percent, respectively (P = 0.02). Peripheral vascular complications necessitating surgery, blood transfusion, or both were more frequent after stenting than after balloon angioplasty (13.5 vs. 3.1 percent, P<0.001). The mean hospital stay was significantly longer in the stent group than in the angioplasty group (8.5 vs. 3.1 days, P<0.001).

Conclusions. Over seven months of follow-up, the clinical and angiographic outcomes were better in patients who received a stent than in those who received standard coronary angioplasty. However, this benefit was achieved at the cost of a significantly higher risk of vascular complications at the access site and a longer hospital stay. (N Engl J Med 1994;331:489-95.)

IMPLANTATION of an intracoronary stent in conjunction with balloon angioplasty is not only highly effective in treating acute vessel closure due to balloon-induced dissection, but it may also reduce the rate of restenosis.[1-4] Unfortunately, all stents currently available are metallic and thus thrombogenic, a problem that necessitates anticoagulation therapy.[5,6] This therapy exposes the patient to an increased risk of major bleeding and vascular complications, which may prolong the hospital stay.[7] Despite these drawbacks and although the superiority of stent implantation over standard balloon angioplasty has not yet been proved, stenting has been used increasingly. Therefore, we conducted a multicenter, randomized study comparing stent implantation and balloon angioplasty with respect to their safety and efficacy

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*The remaining investigators in the Benestent Study Group are listed in the Appendix.

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in patients with stable angina pectoris and a single new lesion in a coronary artery.

Methods

Selection of Patients

Patients scheduled to undergo coronary angioplasty because of stable angina due to a single new lesion in a coronary artery were eligible for the study if they had no contraindication to anticoagulant or antiplatelet therapy and if they were also suitable candidates for coronary bypass surgery. The target lesion needed to be less than 15 mm long and to be located in a vessel more than 3 mm in diameter that supplied normally functioning myocardium. Patients with an ostial lesion, a lesion at a bifurcation, or a lesion in a previously grafted vessel were excluded from the study, as were patients in whom an intracoronary thrombus was suspected.

The study was carried out according to the principles of the Declaration of Helsinki. Oral or written informed consent according to local practice was obtained for every patient.

Randomization

Patients were randomly assigned by telephone from a central office to either implantation of a Palmaz–Schatz stent or balloon angioplasty. To ensure an equal distribution of treatments in each center, we developed the randomization sequence on a site basis in blocks of six treatment assignments.

Balloon Angioplasty and Stent Implantation

Balloon angioplasty and stent implantation were performed according to standard clinical practice by the femoral approach. The stent was deployed by inflating a balloon over which the collapsed stent was fitted. Inflation of the balloon expanded the stent. After the implantation of the stent, the stented area was often dilated further by standard balloon angioplasty. All patients received 250 to 500 mg of aspirin daily and 75 mg of dipyridamole three times a day; this treatment was started the day before the procedure and was continued for six months. During the procedure, patients receiving a stent were treated with a continuous infusion of dextran (1000 ml) and a bolus dose of 10,000 U of heparin, repeated if necessary, followed by a combination of heparin and oral anticoagulation therapy (with warfarin) after the removal of the sheath and titrated by measuring the prothrombin time and either the activated partial-thromboplastin time or the activated clotting time. The dose of heparin was decreased progressively after the prothrombin time had been in the therapeutic range (international normalized ratio, 2.5 to 3.5) for at least 36 hours. Warfarin therapy was continued for three months. The patients who underwent balloon angioplasty received only 10,000 U of heparin during that procedure, followed by an additional bolus dose or a continuous infusion if deemed necessary. In addition, both treatment groups received calcium antagonists until discharge from the hospital.

Clinical and Angiographic Follow-up

Patients were seen in the outpatient clinic after one, three, and six months for an interview, physical examination, and electrocardiogram. Exercise testing was performed before the second cardiac catheterization and coronary angiography at six months. If a revascularization procedure involving the treated segment had been performed before the six-month angiography, the most recent angiogram obtained before this intervention, if available, was used as the follow-up angiogram, regardless of the timing of the second intervention. If the time to follow-up angiography was less than three months and no second intervention was performed, the patient was asked to undergo angiography again at six months. In the absence of a second angiogram at six months, the angiogram obtained most recently within the previous three months was used, if available, provided that no end point had occurred.

Three angiograms were obtained for each patient — one just before the intervention, one immediately after, and one at follow-up. All the angiograms were analyzed by the Cardiovascular Angiography Analysis System and sent to the core laboratory (Cardialysis, Rotterdam, the Netherlands). To standardize the method of data acquisition and to ensure the exact reproducibility of the angiograms performed after the intervention and at follow-up, measurements were made as described earlier.[8]

End Points

The primary clinical end points were whichever of the following occurred first: death, a cerebrovascular accident, myocardial infarction, bypass surgery, or a second percutaneous intervention involving the previously treated lesion between the time of the initial procedure and the angiography performed at 6 months (±4 weeks) (or at 7 months if no angiography was performed at 6 months). The indication for a second intervention or for bypass surgery had to be substantiated by symptoms or by electrocardiographic or scintigraphic evidence of myocardial ischemia at rest or during exercise. All events were reviewed by the critical-event committee, which was unaware of the treatment assignments.

Death was defined to include all deaths, regardless of cause. Cerebrovascular accidents occurring in patients receiving anticoagulant therapy were considered to be intracranial hemorrhages unless unequivocally demonstrated otherwise. Myocardial infarction was diagnosed if there were new pathologic Q waves according to the Minnesota Code[9] or if there was an increase in serum creatine kinase to more than twice the normal value, together with a pathologic increase in myocardial isoenzymes. Bypass surgery was defined to include emergency or elective bypass surgery involving the previously treated segment. Emergency bypass surgery was defined as involving an immediate transfer from the angioplasty suite to the operating room during the initial phase of treatment. "Bailout" stent implantation was defined as the placement of a stent in the event of Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1 flow after angioplasty or in the case of worsening of the base-line TIMI flow by one grade.[10] In all instances, prolonged balloon angioplasty had to be attempted before bailout stenting was considered. By design, stent implantation as a bailout procedure was considered equivalent to emergency bypass surgery but was removed retroactively from the analysis of primary end points, since it is currently perceived as an integral part of an angioplasty strategy. Only the untoward clinical events associated with such stenting were counted as end points. Second interventions were those involving a previously treated lesion that followed the initial procedure, which was considered complete when the guiding catheter was removed from the arterial sheath. Revascularization (surgical or percutaneous) involving other coronary arteries did not constitute an end point.

The primary angiographic end point was the minimal luminal diameter at follow-up. For each treated segment, this value was calculated from the mean values obtained in multiple matched projections.

Secondary end points included (1) the angiographic success rate, defined as the rate of achievement of less than 50 percent stenosis on visual assessment; (2) the procedural success rate, defined as the rate of achievement of less than 50 percent stenosis on quantitative assessment, without the occurrence of clinical events during the hospital stay; (3) the functional class according to the classification of the Canadian Cardiovascular Society at six months or at the time of intercurrent angiography and second intervention; (4) the results of exercise testing at six months or earlier, if clinically indicated; (5) the rate of restenosis (stenosis ≥50 percent at follow-up) at six months.

Power Calculations and Statistical Analysis

At the outset of the study, the size of the required sample (428 patients) was based on an assumed rate of clinical events of 30 percent in the angioplasty group and a reduction of that rate by 40 percent in the stent group (by a two-sided test with an alpha error of 0.05 and a power of 0.80). To compensate for unsuccessful interventions and losses to follow-up, the sample was enlarged by 10 percent (to 470 patients). In addition, to adjust for a loss of power due to a planned interim analysis, the sample was increased by another 10 percent, reaching a final size of 520 patients.[11]

The main clinical analysis consisted of a single comparison be-

tween the two study groups with respect to the primary clinical end point, regardless of its time of occurrence; this analysis involved all randomized patients with the exceptions of three patients found after randomization not to be eligible and of one patient who withdrew informed consent for further treatment and follow-up according to the intention-to-treat principle. The clinical events were ranked according to the highest category of severity on the following scale: death, cerebrovascular accident, myocardial infarction, emergency bypass surgery, elective bypass surgery, and repeat percutaneous intervention.

The main angiographic analysis consisted of a single comparison between the two study groups with respect to minimal luminal diameter and was performed according to the intention-to-treat principle.

Continuous variables are expressed as means ±SD and were compared by the unpaired Student's t-test. The chi-square test with Yates' correction was used to compare proportions. Discrete variables are expressed as counts and percentages and are compared in terms of relative risks (for stenting as compared with angioplasty), with 95 percent confidence intervals calculated by the formula of Greenland and Robins.[12] All statistical tests were two-tailed.

Results

Characteristics of the Patients

Between June 1991 and March 1993, 520 patients were randomly assigned to stent implantation (262 patients) or balloon angioplasty (258 patients) at 28 participating centers. Of these 520 patients, 4 were excluded from further analysis, 3 in the stent group and 1 in the angioplasty group. One patient withdrew his informed consent and left the hospital without receiving treatment, two other patients did not undergo coronary revascularization because their lesions proved to be unimportant during on-line quantitative coronary angiography at the time of the intended intervention, and one patient participated in another study with an investigational drug. There were no differences in base-line characteristics between the two study groups (Tables 1 and 2).

Table 1. Base-Line Clinical Characteristics of the 516 Patients Included in the Intention-to-Treat Analysis.*

Characteristic	Angioplasty (N = 257)	Stent (N = 259)
Age (yr)	58±10	57±9
Weight (kg)	79±13	78±11
Height (cm)	171±9	171±8
	no. (%)	no. (%)
Male sex	212 (82)	207 (80)
Ever smoked	124 (48)	119 (46)
Current smoker	60 (23)	62 (24)
Diabetes mellitus	16 (6)	17 (7)
Previous conditions		
Myocardial infarction	48 (19)	52 (20)
Coronary-artery bypass grafting	5 (2)	0
Angioplasty	8 (3)	5 (2)
Hypertension	89 (35)	80 (31)
Hypercholesterolemia	95 (37)	89 (34)
Stroke	6 (2)	6 (2)
Peripheral vascular disease	8 (3)	10 (4)
Exertional angina (CCS class)†		
I	9 (4)	9 (3)
II	75 (29)	82 (32)
III	130 (51)	125 (48)
IV	20 (8)	16 (6)
None	23 (9)	27 (10)
Mixed	89 (35)	89 (34)

*Plus-minus values are means ±SD.

†According to the classification system of the Canadian Cardiovascular Society (CCS).

In-Hospital Clinical Outcomes

Of the remaining 259 patients randomly assigned to receive stents, 14 (5.4 percent) did not receive a stent but were treated successfully with balloon angioplasty. The reasons for this crossover were the withdrawal of informed consent in five, the physician's preference because of the patient's unfavorable anatomy (e.g., small vessel size) or angiographic evidence of thrombus in three, and failure to cross the lesion with the stent in six. In addition, stent implantation was unsuccessful in 10 patients: 6 because the lesion was not dilated beforehand and 4 because the stent could not be deployed. Of these 10 patients, 8 underwent bypass surgery that was urgent in 3 and elective in 5. The remaining two patients, who unexpectedly had totally occluded coronary arteries that could not be recanalized, were treated medically.

Of the 257 remaining patients randomly assigned to balloon angioplasty, 13 (5.1 percent) received stents for the following reasons: acute vessel closure in 1, flow-limiting dissection in 11, and a suboptimal angiographic result in 1. Of these 13 patients, 2 were referred for urgent bypass surgery and 1 had a non–Q-wave myocardial infarction. In addition, three other patients who had complicated balloon angioplasty and in whom no bailout stent implantation was attempted underwent urgent bypass surgery. Therefore, the angiographic success rate was 96.9 percent in the stent group and 98.1 percent in the angioplasty group, whereas the procedural success rates were 92.7 and 91.1 percent, respectively.

The ranking and the total number of clinical events occurring in the hospital are shown in Table 3. The composite rate for all in-hospital events was similar in both groups (16 events or 6.2 percent in the angioplasty group vs. 18 events or 6.9 percent in the stent group; relative risk, 1.12; 95 percent confidence interval, 0.58 to 2.14). There were no in-hospital deaths in either group; one patient treated with balloon angioplasty had an intracranial hemorrhage. There was no difference between groups in the incidence of Q-wave and non–Q-wave infarction (3.1 percent in the angioplasty group vs. 3.4 percent in the stent group; relative risk, 1.12; 95 percent confidence interval, 0.44 to 2.85) or in the need for urgent or elective cardiac surgery or second angioplasty during the hospital stay (2.7 percent in the angioplasty group vs. 3.5 percent in the stent group; relative risk, 1.28; 95 percent confidence interval, 0.48 to 3.37).

Angiographically documented stent thrombosis during the hospital stay occurred in 3.5 percent of patients, an incidence similar to that of subacute vessel closure after balloon angioplasty (2.7 percent). It is noteworthy that no stent thrombosis occurred in the 13 patients treated with a bailout stent. However, the incidence of bleeding and vascular complications was

significantly higher after stent implantation than after balloon angioplasty (13.5 vs. 3.1 percent; relative risk, 4.34; 95 percent confidence interval, 2.05 to 9.18; P<0.001).

The mean hospital stay was 8.5 days in the stent group and 3.1 days in the angioplasty group (P<0.001).

Clinical Outcomes at Seven Months

The numbers of various types of clinical events at seven months among all 516 patients are shown in Table 3. A primary clinical end point was reached by 76 of the 257 patients randomly assigned to balloon angioplasty (30 percent), as compared with 52 of the 259 patients randomly assigned to stent implantation (20 percent) (relative risk, 0.68; 95 percent confidence interval, 0.50 to 0.92; P = 0.02). This difference in long-term clinical outcome is shown in the cumulative distribution curves for the primary clinical end point in both treatment groups (Fig. 1D). The favorable long-term outcome in the stent group was also partly reflected in the difference between the two groups in functional class at the time of the second angiography (Table 4). The most striking difference in clinical outcomes was the significantly reduced need for an elective second revascularization by means of percutaneous intervention involving the target lesion. There was a 42 percent reduction favoring stent implantation.

During the study, three patients died, one in the

Table 2. Angiographic Characteristics of the 516 Patients Included in the Intention-to-Treat Analysis and Characteristics of the Procedures They Underwent.*

Characteristic	Angioplasty (N = 257)	Stent (N = 259)
	number (percent)	
Artery dilated		
Right coronary	72 (28)	60 (23)
Left anterior descending	159 (62)	165 (64)
Left circumflex	26 (10)	34 (13)
Type of lesion†		
Concentric	118 (46)	130 (50)
Eccentric		
IA	33 (13)	34 (13)
IB	62 (24)	57 (22)
IIA	10 (4)	10 (4)
IIB	13 (5)	10 (4)
Tandem	0	1 (0.4)
Multiple irregularities	21 (8)	16 (6)
Occluded (TIMI 0 or 1)‡	5 (2)	9 (3)
Calcified	27 (11)	29 (11)
Length (mm)	6.96±2.57	7.06±2.56
Thrombus after procedure§	10 (4)	3 (1)
Dissection¶		
No	145 (56)	215 (83)
Type A	43 (17)	21 (8)
Type B	57 (22)	16 (6)
Type C	9 (4)	5 (2)
Type E	1 (0.4)	1 (0.4)
Type F	2 (0.8)	0
Nominal size, stent or balloon (mm)	3.29±0.38	3.31±0.34
Balloon/stent artery ratio	1.12±0.15	1.12±0.15
Largest balloon size (mm)‖	3.30±0.38	3.40±0.40
Maximal pressure (atmospheres)	9±3	10±8
Total inflation time (sec)	399±359	180±178

*The interobserver and intraobserver variability of these morphologic measures has previously been reported by the core laboratory.[13] Plus–minus values are means ±SD.

†According to the classification system of Ambrose et al.[14]

‡According to the TIMI Study Group.[10]

§According to the definition of Ellis et al.[15]

¶According to the classification system of Dorros et al.[16]

‖Nominal size.

Table 3. Frequency of Primary Clinical End Points in the Hospital and at Seven Months in Descending Order of Severity, Total Number of Events, and Quantitative Comparison of Immediate and Long-Term Angiographic Results.*

Event	Angioplasty (N = 257)	Stent (N = 259)	Relative Risk (95% CI)
	number (percent)		
Death			
In hospital	0	0	—
At 7 mo	1 (0.4)	2 (0.8)	1.98 (0.18–21.75)
All events	1 (0.4)	2 (0.8)	1.98 (0.18–21.75)
Cerebrovascular accident			
In hospital	1 (0.4)	0	—
At 7 mo	2 (0.8)	0	—
All events	2 (0.8)	0	—
Q-wave MI			
In hospital	2 (0.8)	5 (1.9)	2.48 (0.49–12.67)
At 7 mo	4 (1.6)	7 (2.7)	1.74 (0.51–5.86)
All events	5 (1.9)	7 (2.7)	1.39 (0.45–4.32)
Non–Q-wave MI			
In hospital	6 (2.3)	4 (1.5)	0.66 (0.19–2.32)
At 7 mo	6 (2.3)	4 (1.5)	0.66 (0.19–2.32)
All events	7 (2.7)	4 (1.5)	0.57 (0.17–1.91)
Urgent CABG			
In hospital	4 (1.6)	5 (1.9)	1.24 (0.34–4.57)
At 7 mo	4 (1.6)	5 (1.9)	1.24 (0.34–4.57)
All events	5 (1.9)	6 (2.3)	1.19 (0.37–3.85)
Elective CABG			
In hospital	0	3 (1.2)	—
At 7 mo	6 (2.3)	8 (3.1)	1.32 (0.47–3.76)
All events	6 (2.3)	10 (3.9)	1.65 (0.61–4.48)
Repeat PTCA			
In hospital	3 (1.2)	1 (0.4)	0.33 (0.03–3.16)
At 7 mo	53 (20.6)	26 (10.0)	0.49 (0.32–0.75)
All events	60 (23.3)	35 (13.5)	0.58 (0.40–0.85)
Any event			
In hospital	16 (6.2)	18 (6.9)	1.12 (0.58–2.14)
At 7 mo	76 (29.6)	52 (20.1)	0.68 (0.50–0.92)

Variable†	Angioplasty (N = 240)	Stent (N = 237)	P Value
	mean ±SD		
Reference diameter (mm)			
Before	3.01±0.46	2.99±0.45	NS
After	3.09±0.44	3.16±0.43	0.045
Follow-up	3.05±0.49	2.96±0.48	0.04
Minimal luminal diameter (mm)			
Before	1.08±0.31	1.07±0.33	NS
After	2.05±0.33	2.48±0.39	<0.001
Follow-up	1.73±0.55	1.82±0.64	0.09‡
Stenosis (%)			
Before	64±10	64±10	NS
After	33±8	22±8	<0.001
Follow-up	43±16	38±18	0.003
Restenosis rate (%)	32	22	0.02
Gain (mm)	0.97±0.39	1.40±0.44	<0.001
Loss (mm)	0.32±0.47	0.65±0.57	<0.001
Net gain (mm)	0.65±0.59	0.75±0.66	0.09

*"All events" refers to the total count of events at seven months (i.e., if a patient required repeat angioplasty and later coronary-artery bypass grafting, the total count at seven months would reflect both events, not just the first that occurred). CI denotes confidence interval, MI myocardial infarction, CABG coronary-artery bypass graft, PTCA percutaneous transluminal coronary angioplasty, and NS not significant.

†Reference values are the interpolated diameters of normal vessels; gain, the minimal luminal diameter after the procedure minus the value obtained before the procedure; loss, the minimal luminal diameter after the procedure minus the follow-up value; and net gain, the minimal luminal diameter at follow-up minus the value obtained before the procedure.

‡P = 0.08 and P = 0.03 for the difference in minimal luminal diameter between the two study groups at follow-up when the pre-intervention lumen and vessel size, respectively, were used as covariates.

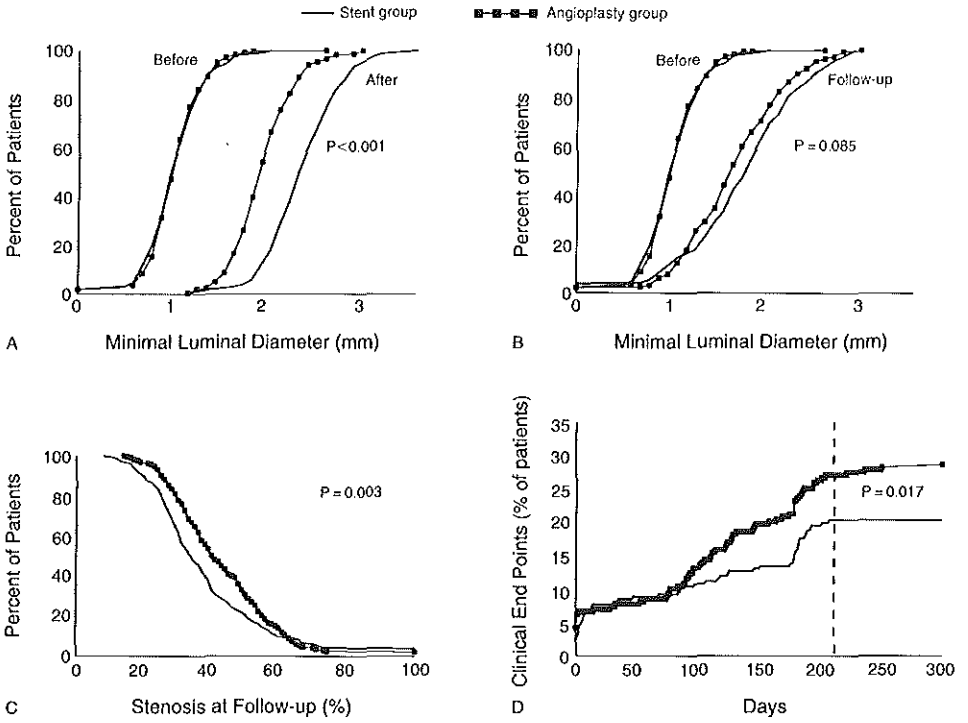

Figure 1. Cumulative Frequency Distribution Curves for the Two Study Groups, Showing Minimal Luminal Diameters Measured before and after Intervention and at Follow-up, the Percentage of Stenosis at Follow-up, and the Percentage of Patients with Clinical End Points.

Significant differences were apparent that consistently favored the stent group over the angioplasty group with respect to the increased minimal luminal diameter at intervention (Panel A) and follow-up (Panel B), the percentage of stenosis at follow-up (Panel C), and the incidence of major clinical events (Panel D). The vertical dashed line in Panel D indicates the end of the study.

angioplasty group and two in the stent group. One patient treated with balloon angioplasty committed suicide four months after the intervention. Two other patients died two and three weeks after successful stent implantations. In the first of these patients, death was preceded by chest pain associated with ST-segment elevation and was therefore thought to be related to a subacute occlusion. In the second patient, the cause of death was hypovolemic shock during surgical repair of an arteriovenous fistula. Although the stent was patent at the time of the pathological examination, the death was considered to be related to the stent.

Angiographic Analysis

Angiographic follow-up data were obtained for 93 percent of the eligible patients (Table 3). The minimal luminal diameter at follow-up was greater after stent implantation than after balloon angioplasty (1.82±0.64 vs. 1.73±0.55 mm, P = 0.09; median difference, 0.17 mm). The cumulative distribution of the minimal luminal diameter and percentage of stenosis are shown in Figure 1A, B, and C. The incidence of restenosis (the criterion for which was ≥50 percent stenosis) was 22 percent after stent implantation as compared with 32 percent after balloon angioplasty (P = 0.02).

Discussion

We found that implantation of coronary stents in patients with stable angina and a single new coronary-artery lesion was associated with a rate of immediate clinical success similar to that of standard balloon angioplasty, but a significantly lower rate of restenosis. This translated into a superior long-term clinical outcome, mainly due to a reduced need for additional percutaneous intervention, at least according to the composite analysis of clinical end points. The advantage of this combined clinical end point is that it leads to a simple estimate of the effect of treatment. However, this analysis ignores the relative effect of various events (i.e., it considers death, a cerebrovascular accident, myocardial infarction, and the like to be equally harmful to the patient) and does not reflect the multiplicity of events that may occur (e.g., in a patient undergoing second angioplasty and surgery and ulti-

Table 4. Functional Class at Seven Months of Follow-up or at the Time of the Intercurrent Intervention for the 516 Patients Included in the Intention-to-Treat Analysis.*

Functional Class†	Angioplasty (N = 257)	Stent (N = 259)
	number (percent)	
0 (Asymptomatic)	170 (66)	190 (73)
I–4	83 (32)	67 (26)
1	10 (4)	12 (5)
2	32 (12)	28 (11)
3	28 (11)	15 (6)
4	13 (5)	12 (5)
Unknown	4 (2)	2 (0.8)

*P = 0.07 for the comparison of functional classes according to treatment group (angioplasty vs. stent).

†The classes shown are those established by the Canadian Cardiovascular Society.

mately dying). To address this shortcoming, a count of all events is included in Table 3.

One of the major drawbacks of studies on the prevention of coronary restenosis is that at follow-up the angiographic knowledge of coronary anatomy may influence the physician's therapeutic decision and artificially increase the number of second interventions. This is especially true when the investigator is not kept unaware of the treatment assignments, as when a new device is tested. To circumvent this possible source of bias, a second intervention was considered an end point in this study only when it was substantiated on the basis of anginal symptoms or objective evidence of ischemia (Table 5). Only two second interventions in the angioplasty group and one in the stent group might not have been justified. Moreover, the fact that the cumulative curves for the composite clinical end points (Fig. 1D) diverged between day 75 and day 150 indicates that the difference in clinical outcome was not artificially driven by the angiographic findings at the time of the second catheterization.

Not unexpectedly, the incidence of major bleeding complications was significantly higher in the stent group (13.5 percent) than in the angioplasty group (3.1 percent). The overall incidence reported in the literature, expressed as a weighted average of groin hematomas and pseudoaneurysms, was 7.5 percent (range, 2.7 to 26 percent) and 4.2 percent (range, 0 to 10.8 percent), respectively.[17]

Table 5. Presence of Clinical Symptoms, Ischemic Signs, and Degree of Stenosis in Patients Who Underwent a Second Intervention at Follow-up.

Variable*	Angioplasty (N = 257)	Stent (N = 259)
No. of patients	59	34†
No. with angina	54	31
No. with ECG changes at rest or during exercise	14	8
No. with neither angina nor ECG changes	2	1
No. with ETT performed	24	14
Percent stenosis — mean ±SD	59±14	66±21‡

*ECG denotes electrocardiographic, and ETT exercise-tolerance test.

†The relative risk as compared with the angioplasty group was 0.57 (95 percent confidence interval, 0.39 to 0.84; P = 0.005).

‡P = 0.05 for the comparison of groups by unpaired Student's t-test.

Another significant difference between the two treatment groups was in the duration of hospitalization. However, Cohen et al. recently showed that length of stay, consumption of resources, and total costs were still substantially greater for bypass surgery than for stenting and that the initially higher in-hospital costs of stent implantation as compared with balloon angioplasty are compensated for by the reduction in subsequent interventions during follow-up.[18,19] The practitioner and the patient must, however, weigh a long hospital stay and a 13.5 percent risk of bleeding and vascular complications against the potential benefit of a reduction in the likelihood of clinical events from 30 percent to 20 percent.

It may be argued that the difference in drug therapy between the two study groups accounts for the observed differences in angiographic outcome and rate of restenosis. However, a number of clinical studies collectively rule out any beneficial effect of anticoagulant therapy on restenosis in humans.[20-25] Moreover, the degree of angiographically documented luminal loss was significantly higher after stent implantation than after balloon angioplasty (Table 3). Therefore, the beneficial angiographic and clinical effects of stent implantation are explained by the propensity of the stent to achieve a consistently greater increase in luminal diameter immediately after the procedure than is the case with balloon angioplasty, which is inherently limited by the well-described phenomenon of elastic recoil.[3,26]

It should be emphasized that in interpreting the favorable results observed in this trial, the restrictive nature of the criteria for inclusion and exclusion must be kept in mind, and thus the results may not be generalizable to other patients, indications, and types of stents. Finally, bleeding and vascular complications and the prolonged hospitalization remain major drawbacks of stent implantation and continue to hamper its acceptance in clinical practice.

Appendix

The following institutions and investigators participated in the Benestent study. The number of patients enrolled at each center is given in parentheses.

University Hospital San Carlos, Madrid, Spain (76): F. Alfonso, J. Goicolea, R. Hernandez, and A. Iniguez; University Hospital Rotterdam Dijkzigt, Thorax Center, Rotterdam, the Netherlands (57): P.J. de Feyter and M. van den Brand; Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands (50): G.J. Laarman and R. vander Wieken; Universitätsklinikum Rudolf Virchow, Charlottenburg, Berlin, Germany (39): W. Rutsch; Onze Lieve Vrouwe Ziekenhuis, Aalst, Belgium (38): B. de Bruyne; Sahlgrenska Hospital, Goteborg, Sweden (36): P. Albertsson; Clinique Pasteur, Toulouse, France (32): J. Fajadet, S. Doucet, and O. Bar; Sart-Tilman Centre Hospitalier Universitaire, Liege, Belgium (32): V. Legrand; Hôpital de la Citadelle, Liege, Belgium (19): J. Boland; Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina (19): J. Berrocal and R. Piraino; Royal Brompton National Heart and Lung Institute, London (12): N. Buller and K. Priestley; Centro

Cuore Columbus, Milan, Italy (11): L. Maiello; Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (11): E. Eeckhout; Middelheim Ziekenhuis, Antwerp, Belgium (10): F. van den Brande; Gregorio Maranon, Madrid, Spain (10): E. Garcia; Ziekenhuis de Weezenlanden, Zwolle, the Netherlands (8): H. Suryapranata and J. Hoorntje; St. Antonius Ziekenhuis, Nieuwegein, the Netherlands (8): T. Plokker and G. Mast; Hospital Maggiore, Trieste, Italy (8): S. Klugmann, E. Della Grazia, and A. Salvi; Hôpital Cantonal Universitaire, Geneva, Switzerland (7): P. Urban and E. Camenzind; Academisch Ziekenhuis Groningen, Groningen, the Netherlands (6): P. den Heijer and R. van Dijk; Academic Medical Center, Amsterdam, the Netherlands (6): J. Piek and K. Koch; Christian Albrechts University, Kiel, Germany (6): R. Simon and G. Herrmann; Centre Cardiologique du Nord, Paris (5): M.C. Morice and T. Royer; St. James Hospital, Dublin, Ireland (5): P. Crean; Catharina Ziekenhuis, Eindhoven, the Netherlands (3): H. Bonnier, J. Koolen, and F. Bracke; Cliniques Universitaires St. Luc, Université Catholique de Louvain, Brussels, Belgium (2): W. Wijns; Centre Hospitalier Régional et Universitaire, Nancy, France (2): N. Danchin and Y. Juillière; and the Polyclinique Volney, Rennes, France (2): C. Bourdonnec.

Ethics and Safety Committee: F. Verheugt, Free University Amsterdam, Amsterdam, the Netherlands; J. Tijssen, Academic Medical Center, Amsterdam, the Netherlands; and G. de Backer, State University Ghent, Ghent, Belgium.

Steering Committee: P.W. Serruys (chairman), H. Emanuelsson, G.R. Heyndrickx, P.P.T. de Jaegere, F. Kiemeneij (co-chairman), C. Macaya, J. Marco, and P. Materne.

Critical Event Committee: F. Kiemeneij (chairman), P.W. Serruys, P.P.T. de Jaegere, P.J. de Feyter, and P. van den Heuvel.

Angiographic Assessment Committee: P.P.T. de Jaegere (chairman), P.W. Serruys, W. Rutsch, B. de Bruyne, and V. Legrand.

Exercise Testing Committee: V. Legrand (chairman), G. Laarman, and N. Danchin.

Data Coordinating and Analysis Center and Quantitative Angiographic Core Laboratory: Cardialysis, Rotterdam, the Netherlands: M. Morel, A.G. Azar, G.A. van Es, J.P. Herrman, R. Melkert, J. Pameyer, and L.M. Rodenburg.

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CHAPTER 3.1

TWO MAJOR CLINICAL PROBLEMS

SUBACUTE STENT THROMBOSIS AND BLEEDING COMPLICATIONS

MULTIVARIATE ANALYSIS FOR PREDICTORS FOR SUBACUTE STENT THROMBOSIS AND BLEEDING COMPLICATIONS IN THE BENESTENT-I STUDY

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Multivariate analysis for predictors for subacute stent thrombosis and bleeding complications in the BENESTENT-I study.

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ABSTRACT

Backgrounds. In the BENESTENT-I study, a Palmaz Schatz stent was implanted in 227 patients with stable angina and a de novo lesion in a native coronary artery and results were compared with balloon angioplasty in a randomized fashion. To determine the risk for stent thrombosis and bleeding complications, a multivariate analysis was performed on the stented population using the per-protocol analysis.
Methods. A multivariate regression analysis was performed controlling for age, gender, diabetes, smoker, hypertension, angina, prior myocardial infarction, left anterior descending artery disease, minimal lumen diameter and reference diameter (pre- and post procedure), lesion length, balloon diameter, inflation pressure, a post procedural dissection and a post procedural bleeding complication.
Results. Subacute thrombosis was encountered in 8 patients (3.5%). Vascular surgery and/or blood transfusion was required in 31 patients (13.7%). Multivariate analysis revealed that female patients had a 3 times higher risk of vascular bleeding complications than males (95% confidence interval: 1.2-7.7). Controlling for the same variables, a patient's probability of experiencing stent thrombosis was lowered when the patient had a large reference diameter pre-procedure, the probability is increased when the patient had a prior myocardial infarction and if the patient had a postprocedural bleeding complication.
Conclusion. Subacute stent thrombosis and bleeding complications form the achillesheel of implantation of metallic coronary stents. The chance for stent thrombosis lowers at large vessel diameters and absence of a previous myocardial infarction and of postprocedural bleeding complications. Female patients are more prone to bleeding complications than male patients.

INTRODUCTION

The purpose of the multicenter randomized BENESTENT I- trial, was to compare safety and efficacy of coronary balloon angioplasty and Palmaz Schatz coronary stenting in patients with stable angina pectoris and a lesion in a native coronary artery (1). Although overall results in terms of restenosis and uneventful follow-up were more favourable in the stented patients, thrombotic stent occlusion (3.5%) and major bleeding complications under intense anticoagulation (13.7%) still remain the achillesheel of this promising new technique (1). In the STRESS- trial, also exploring the differences of outcome of Palmaz Schatz stent implantation and balloon angioplasty, stent thrombosis was encountered in 3.4% and bleeding complications in 7.3% (2). Since no multivariate analysis on these stent related complications has been carried out so far, a multivariate analysis was performed on the patient population in the BENESTENT-I study undergoing a stent implantation. This was done in order to evaluate factors possibly associated with these two complications.

METHODS

Patient population

Subjects who took part in the BENESTENT-I trial, and who were randomized to stent implantation, comprised the study group. The study design has been described in detail elsewhere (1). In short, BENESTENT-I was a multicenter, prospective, randomized, controlled trial, which compared stent placement to balloon angioplasty on immediate angiographic results, incidence of re-stenosis and long-term clinical outcome. After randomization, angioplasty was performed according to the routine of the participating physician. Palmaz Schatz stent implantation was performed with either the Stent Delivery System (3) or with bare stents, after predilatation of the stenosis, in patients with stable angina pectoris and a single de novo lesion in a native coronary artery. If necessary, implantation was followed by secondary stent dilatations in order to improve stent deployment and angiographical results. All patients received the "classical" regimen: heparin, dextran, 250-500 mg daily acetylsalicylic acid, dipyridamole 75 mg tid and anticoagulants. Between June 1991 and March 1993, 259 patients were randomized to stent implantation and 257 to balloon angioplasty.

Coronary angiography

Patients were seen at the outpatient clinic at 1, 3 and 6 months for an interview, physical examination and electrocardiography. Qualitative and quantitative coronary analysis was performed on pre- and post-procedural angiograms, and those obtained at 6 months, by the automated Cardiovascular Angiography Analysis System (4) under standardized circumstances. If a revascularization procedure involving the treated segment had been performed before the 6 month repeat angiography, the last angiogram obtained before this intervention, if available, was used as the follow-up angiogram, irrespective of the timing of repeat intervention (hours, days, weeks). If the time to follow-up angiography was less than 3 months and no repeat intervention was performed, the patient was asked to undergo another angiography at 6 months. In the absence of a 6 month repeat angiogram, the last angiogram obtained within the previous 3 months, if available, was used provided that no end point had occurred.

Definition of clinical events

1. Bleeding complications
   All patients were considered to have a major bleeding complication in the event of blood transfusion and/or vascular surgery.

2. Thrombotic stent occlusion
   Was defined to occur when a patient experienced a stent thrombosis within the hospital stay.

3. Angiographic endpoints
   The angiographic end point included 1) the minimal lumen diameter at follow-up as determined by quantitative angiography. For each dilated or stented segment, the minimal lumen diameter was calculated from the mean values of multiple projections which had been identically matched pre and post intervention and at follow-up; 2) percent diameter stenosis (after device) is the ratio of the minimal lumen diameter and reference diameter.

Statistical analysis

Patients in the trial randomized to balloon angioplasty were not included in this analysis for obvious reasons: patients randomized to the stent group received anticoagulants and therefore were more prone to bleeding complications than the balloon angioplasty group who received no anticoagulants.

Analysis included patients who actually received a stent implantation, i.e. using the "per protocol" analysis. Continuous variables were expressed as means and standard deviations. Discrete variables were expressed as counts and percentages.

Multivariate analysis
A multivariate logistic regression analysis was used to estimate the relative risks (RR) and 95% confidence intervals (CI). The incidence rates obtained from the model maybe viewed as relative risks, i.e., the risk of event relative to the reference risk factor category controlling for the other risk factors. The precision of the relative risks were described by means of 95% confidence intervals.

RESULTS

Study population
From the 259 patients who were randomized to stent implantation, 14 patients did not receive a stent for several reasons (withdrawal of consent, physician's preference, evidence of thrombus or inabilaty to cross the lesion with a stent). In another 10 patients, stent implantation failed. Eight patients refused a 6-months angiographic follow-up. In total 227 patients were stented according to the allocation.
The baseline clinical characterisitics are given in Table 1, and the angiographical characteristics are submitted in Table 2.

Table 1. Baseline characteristics of 227 patients randomized to stent implantation

	n	%
Age (years ± sd)*	57± 9	
Male gender	189	83
Current smoker	54	24
Diabetes Mellitus	15	7
Hypertension	70	31
Hypercholesterolemia	80	36
Prior myocardial infarction	43	19
Prior CABG	0	0
Prior PTCA	4	2
Prior stroke	6	3
History of peripheral vascular disease	8	4
Exterional angina		
CCS I	7	4
CCS II	66	33
CCS III	112	56
CCS IV	16	8
Non exertional angina	994	

* Means and standard deviations are indicated
CABG, Coronary Artery Bypass Graft; CCS, Canadian Cardiovascular Society angina classification; PTCA, Percutaneous Transluminal Coronary Angiography

Clinical endpoints
Table 3 shows the primary clinical end-points. Bleeding complications requiring blood transfusions or vascular surgery were encountered in 31 patients (13.7%). Subacute stent thrombo-

sis was angiographically demonstrated in 8 patients (3.5%).
Results of multivariate analysis of predictors for bleeding complications is represented in Table 4. Controlling for all other extraneous variables, female patients had at least a 3 times higher risk of bleeding complications than male. The large confidence interval (1.2-7.7) is explained by the small number of events involved in the analysis.
In Table 5 the prediction of stent thrombosis is given. Controlling for all other extraneous variables, patients who had a post procedural bleeding complication were at 28 times higher risk for developing of stent thrombosis. Patients with a prior myocardial infarction have more than 250 times a higher risk of stent thrombosis than patients with no history of myocardial infarction. However, although the risk is statistically significant, the large confidence interval (4.4;>1000) indicates the small number of patients with subacute stent thrombosis.
Furthermore, the data indicate for every unit decrease in reference diameter pre procedure, the risk for stent thrombosis increases by $8.8*10^{-7}$ i.e., the larger the pre-procedural reference diameter, the smaller is the probability for a stent thrombosis.

Table 2. Angiographic and procedural characteristics of 227 stented patients

	n	%
LAD	148	65
Lesion length	7.0± 2.0	
TIMI flow		
0 or 1	7	3
2 or 3	220	97
Dissection		
No	195	86
Type A or B	29	13
Type C or D or E or F	3	1
Nominal stent and balloon size (mm ± sd)	3.41± 0.40	
Balloon/stent artery ratio (± sd)	1.12± 0.15	
Maximal pressure (atm ± sd)	10.1± 7.8	
Total inflation (secs ± sd)	163± 144	
Reference vessel diameter (mm ± sd)		
Pre-procedure	3.00± 0.44	
After device	3.17± 0.42	
Angiographic follow-up	2.97± 0.48	
MLD (mm ± sd)		
Pre-procedure	1.07± 0.33	
After device	2.51± 0.36	
Angiographic follow-up	1.85± 0.64	
DS (% ± sd)		
Pre-procedure	64± 10	
After device	21± 7	
Angiographic follow-up	38± 18	

DS, diameter stenosis; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; MLD, minimal luminal diameter; RCA, right coronary artery; * see reference 5; ** see reference 6

Table 3. Bleeding complications and thrombotic stent occlusion

	n	%
Bleeding Complications	31	13.7
Vascular surgery		
Pseudoaneurysm	14	
Arteriovenous fistula	1	
Major haematoma	7	
Gastro-intestinal bleeding	0	
Blood transfusion		
Pseudoaneurysm	1	
Arteriovenous fistula	1	
Major haematoma	6	
Gastro-intestinal bleeding	1	
Thrombotic stent occlusion	8	3.5

Table 4. Prediction of bleeding complications

	Coëfficient	SEcoff.	Rate Ratio	95%, C.I.
Intercept	-2.1	--	--	--
Female	1.1	0.5	3.1	1.2-7.7

SE, standard error; coff, coëfficient; C.I., confidence interval; MI, myocardial infarction; ref, reference.

Table 5. Prediction of stent thrombosis

	Coëfficient	SEcoff.	Rate Ratio	95%, C.I.
Intercept	13.70	--	--	--
Bleeding complications	3.33	1.35	28	2.0;394
Prior MI	5.58	2.09	265	4.4;>1000
Ref. diameter (pre)	- 7.77	3.15	4.2×10^{-4}	8.8×10^{-7};0.20

SE, standard error; coff, coëfficient; C.I., confidence interva; MI, myocardial infarction; ref, reference.

DISCUSSION

Implantation of coronary stents for coronary artery disease aims at improvement and optimalization of coronary geometry in order to reduce the incidence of restenosis of de novo lesions in native coronary arteries (1,2), in venous bypass grafts (7), refractory restenosis (8), and to treat dissections and suboptimal results after balloon angioplasty (9,10,11).
The problems encountered after implantation of metallic stents are two-fold; risk for stent thrombosis requiring aggressive anticoagulation and the associated risk for access site related bleeding complications.
Only 0,6% of anticoagulated patients suffered from subacute stent- occlusion in the multicenter study in elective cases reported by Schatz et al. (12). The highest subacute stent occlusion rates are reported in early literature after stenting for suboptimal angio-plasty, as reported by Schatz et al. (5.3%) [13], Kimura et al. (9.3%([14], Haude et al. (12%) [11], Kiemeneij et al. (23%) [7] and by Fajadet et al. (29.4%0 [15].

The occlusion rates in the electively stented patient groups according to the BENESTENT-I (3.5%)[1] and STRESS trials (3.4%)[2], takes an intermediate position between these two extremes, probably because during the course of this study, achievement of an optimal post procedural result was recognized to be associated with less thrombotic occlusions.
Except for bailout situations, in recent literature the following risk factors for stent thrombosis were recognized. Fischman et al. reported on angiographic predictors of subacute stent thrombosis in a group of 726 patients with a Palmaz Schatz coronary stent (16). Intraprocedural thrombus and persistent dissection as well as suboptimal results after PTCA were associated with an increased risk for subacute thrombosis. Since presence of intracoronary thrombus was considered to be a contraindication for participation in the BENESTENT trial, this risk factor could not be studied in our trial.
We found that small pre-procedural reference diameters (< 3.0 mm) are associated with increased risk for stent thrombosis. Optimal stent expansion, under intravascular ultrasonic guidance, may further decrease the risk for stent thrombosis (17).
Erbel et al. (18) considered suboptimal monitoring of anticoagulation as a risk for stent thrombosis. By introducing monotoring of prothrombin factors F1+2, the incidence of stent thrombosis reduced in their experience. In the multivariate analysis of the BENESTENT study, the intensity of anticoagulation as risk factor for the thrombotic occlusions and bleeding complications could not be assessed, since there was a considerable difference in the laboratory tests used to monitor treatment among institutions. Consequently, the thromboplastin used to measure the prothrombin time were prepared by different methods and therefore their effect on the reduction of the vitamin K clotting factors varied significantly. In order to circumvent the problem of variability in the sensitivity of thromboplastin, the International Nomalized Ratio (INR) should be introduced in subsequent trials (19).
An infarcted area supplied by the target vessel formed a contraindication to participate in this study. However, the presence of a previous myocardial infarction (19%) in other regions was associated with a higher risk for stent occlusion. Mechanisms such as deminished coronary perfusion caused by poor left ventricular function, irrespective the localization of the infarcted region, may have played a role. It should be emphasized however, that only 8 patient had subacute stent thrombosis and that therefore the 95% confidence intervals are very wide.
Of the 8 patients with stent thrombosis, 3 had a bleeding complication, before the stent occluded. Since a bleeding complication forces the clinician towards less aggressive anticoagulation or even to a strategy to reverse anticoagulation, a bleeding may be considered as a risk factor for stent occlusion.
The incidence of puncture site related complications, has been reported to vary between 7.9% of 226 patients in the initial multicenter experience with the Palmaz Schatz stent (12) and 16% of 220 patients in large single center experience (20). In the study of Piana et al., reporting on Palmaz Schatz stenting in vein grafts, vascular repair was necessary in 8.5% and transfusions in an additional 14% (7). Bleeding complications requiring vascular surgery or transfusions was reported in 13.5% of patients after stent implantation in the BENESTENT study (1) and in 8.8% in the STRESS- study (2).
Especially females were at risk for entry site related complications. Despite introduction of new hemostasis techniques (21,22,23,24), the occurence of vascular complications after coronary stenting remains one of the major hazards of this technique. However, groin problems can be circumvented by performing stent implantation via the radial artery, as demonstrated by Kiemeneij et al.. (25,26). In a series of 100 patients, who had a transradial stent procedure attempted, one patient developed a major radial artery related bleeding complication, requiring vascular surgery. Another method to reduce the risk for bleeding complications is the simplification of the anticoagulation regimen after an optimal stent implantation result (17), by combining subcutaneous heparin with oral administration of ticlopidin and acetosalicylic acid (27,28). Although promising results have been reported, this approach requires careful patient selection, since suboptimal stent results, not always appreciated with angiography,

may further increase the risk for stent thrombosis if no adequate anticoagulation is administered. Finally, the implantation of heparin coated stents, by reducing the thrombogenicity of the device, has the potential for a save reduction in systemic anticoagulation, without posing the patient at risk for stent thrombosis (29).

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CHAPTER 4.1

POTENTIAL SOLUTIONS

IMPROVEMENT OF STENT DEPLOYMENT ASSESSED BY INTRAVASCULAR ULTRASOUND

MODE OF DEPLOYMENT OF CORONARY PALMAZ SCHATZ STENTS AFTER IMPLANTATION WITH THE STENT DELIVERY SYSTEM: AN INTRAVASCULAR ULTRASOUND STUDY

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Mode of deployment of coronary Palmaz Schatz stents after implantation with the Stent Delivery System: An intravascular ultrasound study.

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ABSTRACT

Rationale: The Stent Delivery System (SDS) is a sheath covered, Palmaz Schatz stent, mounted on a 3.0, 3.5 or 4.0 mm compliant polyethylene balloon catheter, resisting maximal inflation pressures of 5.7, 6.2 and 6.0 atmospheres respectively. It is postulated that these pressures are too low to obtain optimal stent deployment. Since optimal stent deployment is a prerequisite for optimal short- and longterm outcome, we performed an intravascular ultrasound study to the mode of stent deployment after delivery with the SDS and after high pressure dilatations with low compliant, oversized balloon catheters.
Methods: In 23 patients an intravascular ultrasound study (30 MHz, 4.3 French transducer) was performed to the geometry of 29 stents immediately after delivery with the SDS and after successive high pressure inflations with low compliant balloons.
Results: After delivery with the SDS (3.3 ± 0.4 mm), stent diameter was 3.0 ± 0.4 mm. After high pressure dilatations (12.4 ± 1.4 atm), with low compliant balloons (3.9 ± 0.5 mm), stent diameter increased to 3.4 ± 0.4 mm) {p<0.001}.
Only 8 stents (28%) were completely and symmetrically expanded to the corresponding reference diameter, with good apposition, after delivery with the SDS.
Diameter of incomplete deployed stents (n=16) was 2.8 ± 0.3 mm. After high pressure dilatations with low compliant balloons (3.9 ± 0.5 mm), diameter increased to 3.4 ± 0.4 mm (p<0.001). Now 20 stents (69%) {p=0.004} became completely and symmetrically expanded to a diameter corresponding to the reference diameter.
Conclusion: Most stents are suboptimally deployed after delivery with the stent delivery system. Stent expansion and geometry can be improved by dilatations with low compliant, high pressure, oversized balloons.

INTRODUCTION

In order to increase safety of Palmaz Schatz stent implantation, by reducing the risk for stent loss and stent embolization during attempts to reach and to cross the target lesion, a stent delivery system (SDS) has been developed (Johnson & Johnson Interventional Systems Co, Warren, New Jersy). This system is a preassembled unit, containing a 5F sheath covered, 15 mm Palmaz Schatz stent, mounted on a polyethylene, compliant balloon catheter. The SDS comes in 3 balloon sizes; 3.0, 3.5 and 4.0 mm, all 20 mm in length. Recommended maximal inflation pressures are 5.7, 6.2 and 6.0 atmospheres, respectively. We postulated that these pressures with compliant balloons are too low to obtain optimal stent deployment and geometry, despite satisfactory angiographical results. An example is given in Figure 1. Angiographical appearance improved markedly after stenting with the SDS, for this venous bypass graft stenosis. During intravascular ultrasound, however, the stent appeared to be oval shaped and incompletely deployed. After inflations with a low compliant, high pressure balloon, stent geometry clearly improved ultrasonically, but angiography showed only a subtle change. The Palmaz Schatz stent has a poor radioopacity, so detailed information on the quality of stent deployment cannot be obtained by fluoroscopy and conventional angiography. Since intravascular ultrasound may provide complementary information to angiography, several techniques became guided by intravascular ultrasound; balloon angioplasty (1,2,3), directional (4,5,6) and rotational atherectomy (7) and coronary stent implantation (8,9,10,11,12). Since optimal short- and longterm results of coronary stenting may be depen-

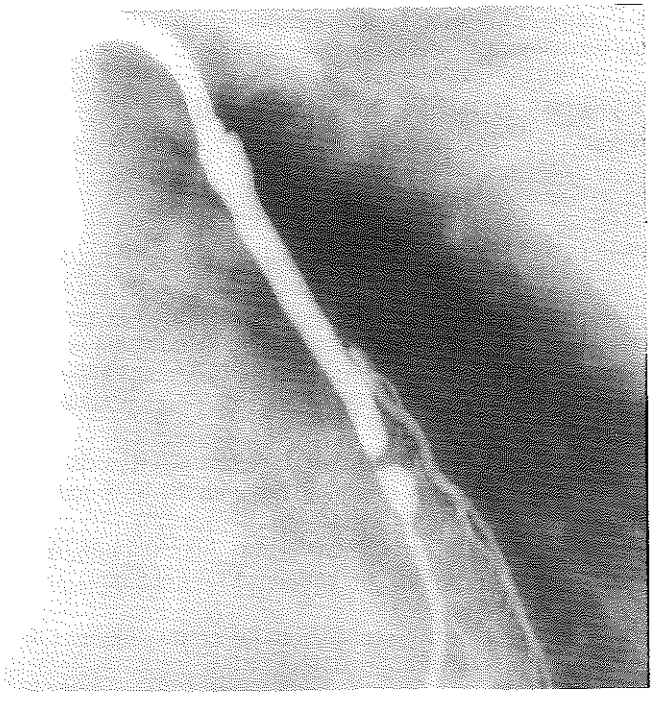

Figure 1a. Severe venous bypass graft stenosis

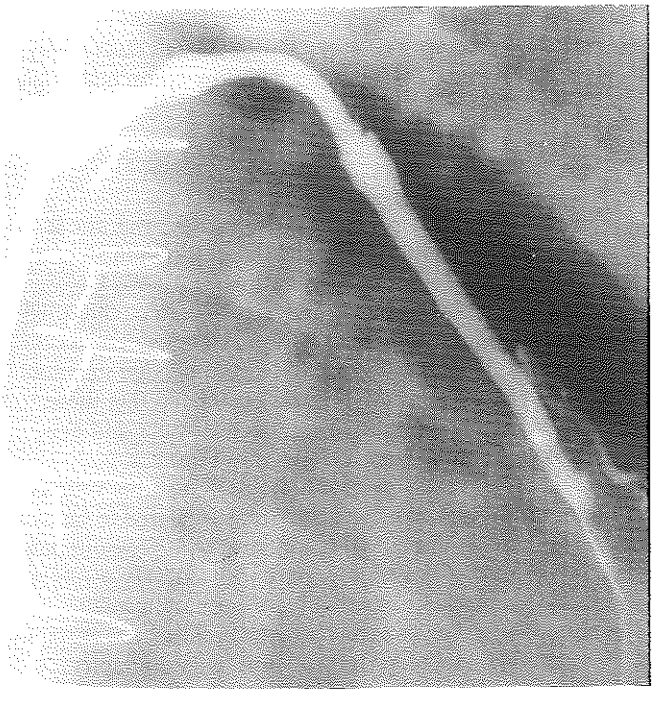

Figure 1b. Angiographically markedly improved after stent implantation by the SDS

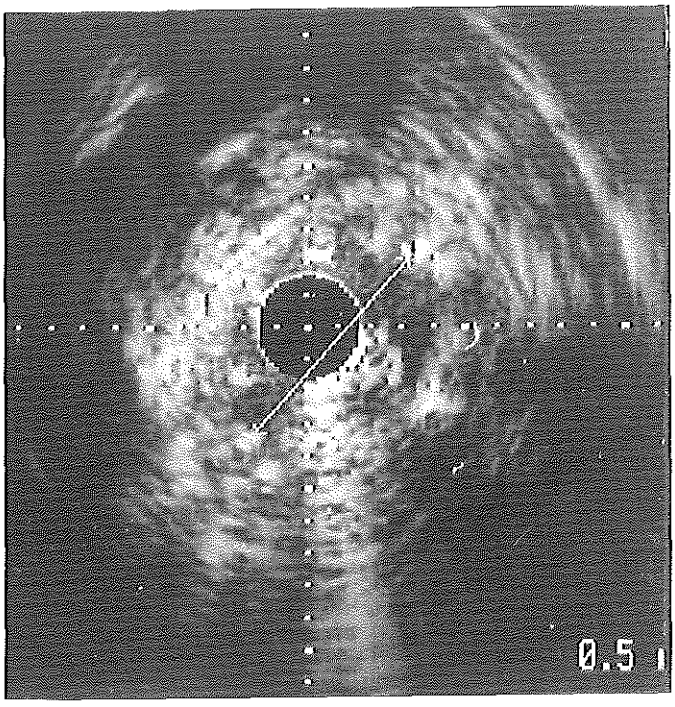

Figure 1c. Oval shaped, incompletely deployed stent, with poor contact against the vessel wall (3.7x2.7 mm)

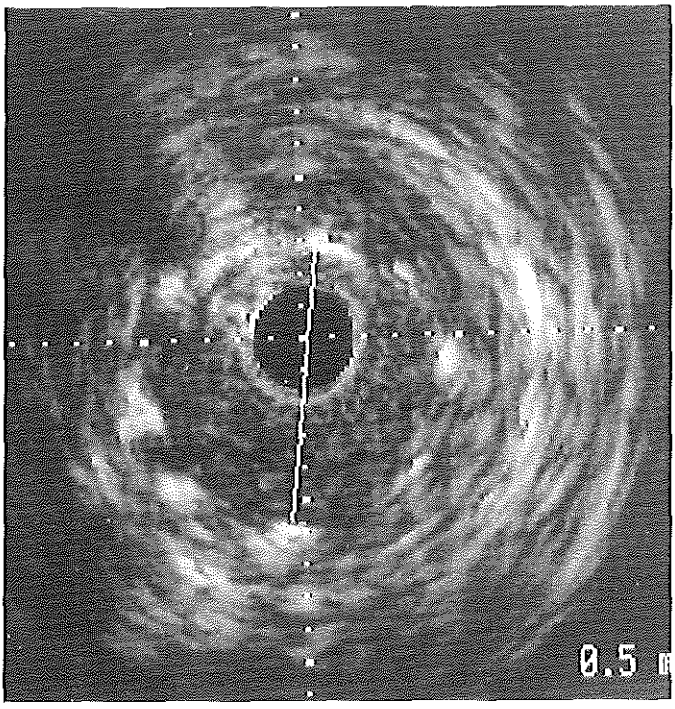

Figure 1d. Circular shaped stent after high pressure dilatation; still poor vessel wall contact at stent diameter of 4.4 mm (no larger balloon available)

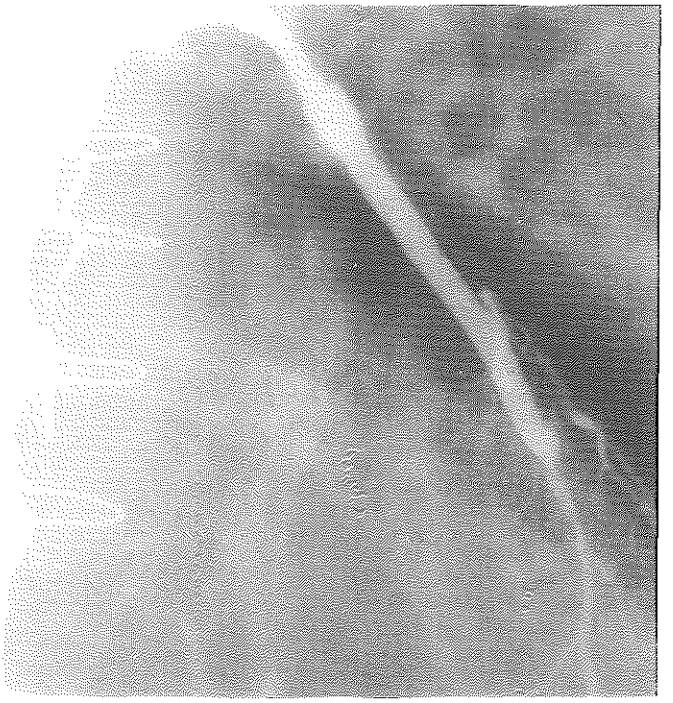

Figure 1e. Slight improvement angiographically

dent on optimal stent delivery and thus maximal acute gain in vessel lumen (7), we performed an intravascular ultrasound study to monitor stent deployment and geometry, after delivery with the SDS and after high pressure dilatations with low compliant balloon catheters.

METHODS

Study population

This study was performed between september 1991 and november 1992. In 27 patients assessment of stent diameters, by intravascular ultrasound, after delivery by the sheath protected system and after post stent dilatations was attempted. In 3 patients the ultrasound transducer could not cross the stent. From one patient (1 stent), ultrasound data were not available for analysis due to technical problems with the imaging device as was the case in another patient, where data were lost from one of the 2 implanted stents. Thus from 23 patients, 29 stents were analysed. Intravascular ultrasound studies were performed after stent implantation in venous coronary bypass grafts (n=9, 39%), the left anterior descending coronary artery (n=6, 26%), the left circumflex coronary artery (n=6, 26%) and in the right coronary artery (n=2, 9%). Baseline characteristics are given in Table I.

Angiography and percutaneous transluminal coronary angioplasty

The x-ray imaging equipment used at our catheterization laboratory is the Philips Poly Diagnost C2, powered by an Optimus M200 generator and equipped with a Digital Cardiac Imaging system (DCI). PTCA and stent implantation were performed in patients receiving acetylsalicylic acid 300 mg daily, nifedipine 30 mg daily , Dextran 50 ml/hr iv to a total of 1 liter. After introducing the arterial sheath 10.000 IU heparin was administered intraarterially, followed by 5.000 IU each hour during the procedure. Intracoronary nitroglycerin 100 micro-

gram was given before the first coronary contrast injection and repeated after stent implantation and before ultrasound analysis.
PTCA was performed in all patients by means of the femoral approach. Super flow guiding catheters with an internal diameter of at least 0.079 inch, were used, in combination with a monorail dilatation system and a 0.014 inch guidewire.

Stent-implantation
Stent implantation in elective cases was preceded by dilatation with an undersized balloon. The stent-loaded balloncatheter was advanced over the guidewire to the obstructing lesion. After careful positioning the protective sheath was withdrawn, followed by stent delivery with the recommended inflation pressures and control angiography. Compared to the coronary artery diameter, the stent was slightly oversized by high pressure dilatations with larger low compliant balloons to compensate for some decrease of the stent-diameter after delivery.

Intravascular ultrasound
A 30-MHz ultrasound transducer, housed in the tip of a 4.3F, 135 cm long rapid exchange catheter was used (Cardiovascular Imaging Systems). An angulated mirror (45°) in the ultrasound transducer was connected to a motor-driven unit, rotating at 1.800 rpm.
The reflected ultrasound beam creates a 360 degrees cross-sectional image, perpendicular to the vessel wall at a rate of 30 frames per second. No ultrasound studies were performed before the initial dilatation, because of expected catheter occlusion of the lumen. Ultrasonic studies were repeated after the last dilatation following stent implantation. The transducer was positioned under fluoroscopy during injections of contrast medium. Ultrasound gain and compression settings were adjusted for optimal visualization of the stent filament reflections in relation to the arterial wall-lumen interface. Images were selected in end-diastole, with optimal coaxial alignment of the ultrasound catheter, to prevent misinterpretation of stentgeometry. The calipers were diametrically placed central from two opposite leading edges of the vessel wall or at the inner surface of the stent filaments. Luminal diameters were recorded as minimal and maximal values. Images were obtained from different sites of the stented segment and from the immediate area from the stent in order to select the optimal balloon size, derived from manufacturer provided tables, plotting balloondiameter against inflation pressures. The reference diameter was defined as the largest vessel diameter adjacent to the stenotic coronary segment. Reference- and stent diameters were determined on-line because it was felt critical to obtain data from real-time images, during careful manipulation of the transducer. Consensus-reading on reference- and stent diameters was performed by at least 2 investigators. The last passage of the ultrasonic catheter was followed by angiographic control of the vessel, to detect possible catheter induced damage.

Definitions
The stent was considered to be symmetrically deployed at a ratio of minimal and maximal stent diameters ≥ 0.9. After delivery with the SDS, complete stent deployment was defined as a stent diameter >90% of the reference diameter or >90% of the nominal SDS balloon diameter. After post stent dilatation a completely deployed stent was defined at a stent diameter >90% of reference diameter or >90% of the final balloondiameter
The stent was considered to be well apposed if no free space between the stentfilaments and the vessel wall was detectable.

Statistics
Values are expressed by mean $\pm$ SD. Differences in stent diameter before and after high pressure balloon inflations were calculated with the t-test. A Chi-square analysis was performed on differences in mode of stent expansion before and after post- stent dilatation. A p- value $<$ 0.05 was considered to be statistically significant.

RESULTS

In all 23 pts good quality images from the stent could be obtained before and after post stent dilatations. Diameters of target segments, balloon catheters and stents are given in Table II.

Table I. Baseline characteristics (N=23)

Male	14	61%
Age	61 ± 9.1	years (median 62; range 44-76)
Functional class		
-Stable angina	18	78%
-Unstable angina	4	18%
-Acute myocardial infarction	1	4%
Indication for coronary stenting		
-Venous bypass graft stenosis	9	39%
-Restenosis	5	22%
-Bailout	7	30%
-De novo, native	2	9%

Diameter analysis for the total study population
Reference diameter of stented segments was 3.6 ± 0.5 mm (median 3.5; range 2.8 - 5.2). The diameter (manufacturer specified) of the selected stent delivery systems (balloon length: 20 mm) was 3.3 ± 0.4 mm (median 3.5; range 3.0 - 4.0) which came close to the reference diameter. After deployment with the SDS, stent diameter was 3.0 ± 0.4 mm (median 2.9; range 2.2 - 3.9). All stents were successively dilated with 20 mm long, high pressure balloons of lower compliance. At inflation pressures of 12.4 ± 1.4 atmospheres (median 12; range 8 - 14), manufacturer specified balloon diameter was 3.9 ± .5 mm (median 3.8; range 3.2 - 4.4). Stent diameter increased to 3.4 ± 0.4 mm (median 3.1; range 2.9 - 4.3) {p<0.001}.

Diameter analysis for improper deployed stents.
Of 29 stents, 16 (55%) stents were smaller in diameter compared to the diameter of the stent delivery system (3.3 ± 0.4 mm {median 3.3; range 3.0 - 4.0}). For this subgroup, stent diameter increased from 2.8 ± 0.3 mm (median 2.8; range 2.2 - 3.5) to 3.4 ± 0.4 mm (median 3.3; range 3 - 4.3) {p<0.001} after post stent dilatations (balloon diameter 3.9 ± 0.5 mm {median 3.8; range 3.2 - 4.4}).

Mode of stent deployment.
Six modes of stent deployment were encountered immediately after deployment with the delivery system (Table II). Ten stents (35%) were incompletely, but symmetrically deployed with poor vessel wall contact (group 1). In group 2, 2 stents (7%) had the same mode of deployment, but were well apposed. Symmetric and complete deployment was seen in 13 stents (45%). Three out of 5 completely deployed stents with poor apposition (group 3) were delivered with an SDS ≤90% of the reference diameter. Only 8 stents (28%) showed initial complete and symmetric expansion to the corresponding reference diameter (group 4).
Asymmetric and incomplete deployment with and without apposition (groups 5 and 6) was encountered in 3 (10%) and 1 (3%) instances, respectively.
High pressure dilatations were performed in the 8 well deployed stents (group 4) in order to obtain maximal stent deployment. However, these stents did not change significantly in dia-

meter (3.1 ± 0.4 and 3.2 ± 0.4 mm respectively; p=0.5). After high pressure dilatations 20 stents (69%) {p=0.004} were symmetrically expanded to a diameter corresponding to the reference diameter. However, 8 stents (28%) were still smaller than the reference diameter, but in 2 cases this could be contributed to an undersized balloncatheter (diameter ≤90% of reference diameter). One stent (3%) remained oval shaped.

Table II. Initial and final stent diameters (SD) in relation to reference diameter (RD), SDS- and post-stent balloon (PSB) diameter.

	RD	SDS	Initial SD	PSB	Final SD
Group 1 (n=10). Initial symmetric, but incomplete deployment, with poor apposition					
Mean	3.6 ± 0.4	3.2 ± 0.2	2.7 ± 0.3	3.7 ± 0.5	3.2 ± 0.3
Median	3.5	3.0	2.7	3.5	3.1
Range	3.0 - 4.5	3.0 - 3.5	2.2 - 3.1	3.3 - 4.4	3.0 - 3.8
Group 2 (n=2). Initial symmetric, but incomplete deployment, with good apposition					
Mean	3.5 ± 0.7	3.5 ± 0.7	3.1 ± 0.6	3.8 ± 0.9	3.6 ± 0.9
Median	3.5	3.5	3.1	3.8	3.6
Range	3.0 - 4.0	3.0 - 4.0	2.7 - 3.5	3.2 - 4.4	3.0 - 4.2
Group 3 (n=5). Initial symmetric, complete deployment, with poor apposition					
Mean	3.6 ± 0.4	3.3 ± 0.3	3.2 ± 0.3	4.0 ± 0.6	3.5 ± 0.6
Median	3.9	3.5	3.2	3.8	3.6
Range	3.1 - 4.0	3.0 - 3.5	2.8 - 3.5	3.4 - 4.4	2.7 - 4.1
Group 4 (n=8). Initial symmetric, complete deployment, with good apposition					
Mean	3.2 ± 0.4	3.3 ± 0.4	3.1 ± 0.4	3.8 ± 0.5	3.2 ± 0.4
Median	3.0	3.3	3.0	3.8	3.1
Range	2.8 - 3.9	3.0 - 4.0	2.8 - 3.9	3.3 - 4.4	2.9 - 3.9
Group 5 (n=3). Initial asymmetric, incomplete deployment, with poor apposition					
Mean	4.4 ± 0.8	3.8 ± 0.3	3.2	4.2 ± 0.4	3.9 ± 0.4
Median	4.3	4.0	3.2	4.4	3.9
Range	3.7 - 5.2	3.5 - 4.0	3.2	3.8 - 4.4	3.6 - 4.3
Group 6 (n=1) Initial asymmetric, incomplete deployment, with good apposition					
	3.5	3.5	2.8	4.4	3.3

Complications

Control angiography following the final ultrasound examination revealed no visible damage to vessel wall or stent and no complications such as distal embolization or spasm could be contributed to the use of the ultrasound transducer.

Follow-up

Subacute stent thrombosis was encountered in 2 patients (9%). One patient had a residual stenosis between two stents, placed for a dissection in the LAD after PTCA. Stent occlusion occured 7 days after the procedure. The other patient had a residual ± 40% stenosis distal from the stent. This patient developed stent occlusion 3 days later. Both patients had successful recanalization by repeat PTCA, followed by bypass surgery. Another patient had coronary bypass surgery the day of successful bailout stent implantation following PTCA of the right coronary artery complicated by an obstructive dissection. This patient required acute thoracotomy for tamponade, caused by perforation of the right ventricle by a temporary pacing elec-

trode. In order to prevent post-operative bleeding complications, the decision was made to bypass the stent in the RCA, allowing a lower level of postoperative anticoagulation. Another patient died 2 weeks after a bailout stent implantation following PTCA of the LAD. This procedure was complicated by a severe groin bleeding, necessitating vascular surgery. In the post-operative phase this patient developed fatal multi-organ failure. Angiographical follow-up at 6.9 ± 4.0 months (range 0.5 to 13.5; median 7.5) after stent implantation, was obtained from 13 of 19 patients (68%) who had an uneventful clinical course. Stent restenosis was encountered in 1 patient (8%), followed by successful repeat PTCA. From 5 out of 6 patients who did not have control- angiography, one year clinical follow-up was obtained from the referring physicians. All these patients were alive and were free of myocardial infarction, coronary bypass surgery, repeat PTCA, and angina. One patient was lost from follow-up.

DISCUSSION

Coronary Palmaz Schatz stent implantation has been shown to reduce restenosis in a selected group of patients with a de novo lesion in native coronary arteries (13,14) and to improve suboptimal results after balloon angioplasty (15,16,17,18,19). The underlying mechanisms may be improved vessel geometry and elimination of intimal flaps. In order to optimize procedural success and safety of the implantation technique, by reducing the risk for stent loss and embolization during attempts to reach the coronary target lesion, a stent delivery system has been introduced. This system, containing a compliant polyethylene balloon catheter, comes in 3 balloon sizes; 3.0, 3.5 and 4.0 mm. The recommended maximal inflation pressures (5.7, 6.2 and 6.0 atmospheres, respectively) are expected to be too low, to achieve optimal stent deployment. Since optimal stent deployment or the maginitude of acute lumen gain may lead to improved short- and longterm success of this technique (7) additional balloon angioplasty after stent implantation with high pressure oversized balloons has been advocated. Based on careful quantitative coronary analysis (edge detection), de Jaegere et al (20) demonstrated improved stent deployment in patients who had post stent dilatations, when compared to patients who did not have additional balloon angioplasty. However, optimal angiographical results of stent implantation have been reported, where intravascular ultrasound demonstrated suboptimal results (8,9,10,11,12).

In the study of Laskey et al, angiographic quantitative analysis in 12 pts undergoing stent implantation revealed an increase of minimal stenosis diameter of 1.8 ± 0.6 mm after balloon angioplasty to 2.8 ± 0.3 mm after Palmaz Schatz stent implantation. Determined by IVUS, fractional plaque area remained unchanged (30 ± 12% and 32 ± 11% respectively). The authors conclude that considerably less improvement was found by IVUS compared to substantial improvement if the residual luminal obstruction was assessed angiographically. Improved acute stent implantation results after oversized balloon angioplasty was demonstrated by intravascular ultrasound in several studies (10,11,12). In the study of Nakamura et.al. (11) the following criteria for optimal stent expansion were defined: 1. Full apposition of the stent against the vessel wall; 2. Lumen symmetry index (minimal diameter/maximal diameter) ≥ 0.7; 3. Stented lumen cross sectional area (CSA) ≥ 60% of the reference vessel CSA. With these 3 criteria applied, optimal stent expansion was obtained in 21% after initial delivery and in 73% after post stent dilatations. In our study, criteria for optimal stent deployment were more rigid. Only 8 stents (28%) were completely and symmetrically expanded with good apposition against the vessel wall, after low pressure delivery with the SDS.

The diameter of incompletely deployed stents increased from 2.8 ± 0.3 mm to 3.4 ± 0.4 mm ($p<0.001$) after post stent dilatations. Complete and symmetric stent expansion, corresponding to the target segment reference diameter increased to 20 stents (69%) {$p=0.004$ when compared to initial expansion}. It remains uncertain if this optimal stent deployment has contributed to the low incidence of restenosis in those patients who had an uncomplicated clinical course (one of 13 patients {8%}) with angiographical follow-up and no clinical signs for restenosis

at 1 year in 5 other patients), since the study population was too small to allow such a conclusion. Several other limitations of this study should be mentioned. Although information on cross-sectional area and plaque area is more relevant than information on diameters, we did not perform area measurements since on-line and off-line automated digitized border tracing was not available. Instead, diameters were assessed on-line by electronic calipers. Also, no analysis was made on plaque- morphology and composition. Differences in plaque components may have been present in patients in which optimal and suboptimal stent deployment. Another limitation of this study is the comparison between actual ultrasonically assessed vessel diameters and stent diameters on the one hand and manufacturer given balloon diameters on the other hand. Manufacturer specified balloon diameters are determined under in vitro conditions. Under circumstances, where vessel wall and obstructing plaque, as well as the stent itself, may considerably influence the extent of balloon expansion under given inflation pressures, real balloon diameters probably are significantly different from nominal diameters. However, the discrepancy between ultrasonically assessed stent diameter and reference diameter after SDS delivery and the suboptimal mode of stent deployment could reliably be demonstrated in our study, as well as the improvement after additional balloon angioplasty. These findings are noteworthy for several reasons. Based on this experience, we now routinely perform additional balloon angioplasty after stent implantation with the SDS, because we expect initial stent deployment to be suboptimal. For clinical practice, this policy can be followed, even without ultrasound control, because of the anticipated improvement in stent deployment and geometry. However, a third balloon is required, when the under-over principle is followed: one undersized balloon for predilatation to allow easy passage of the second, stent- loaded and sheath protected, balloon and the third balloon to obtain an optimal final result. By replacing the current balloon, contained in the stent delivery system, by a non-compliant, high pressure, adequately sized balloon, procedural costs and time can be reduced.

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CHAPTER 4.2

POTENTIAL SOLUTIONS

IMPROVEMENT OF ADJUSTMENT ON ANTICOAGULATION

PRACTICAL VALUE OF PROTHROMBIN FRAGMENT F1+2 ASSESSMENT AFTER CORONARY STENTING

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Practical value of prothrombin fragment F1+2 assessment after coronary stenting.

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ABSTRACT

Objectives. We conducted a prospective study of the relation between prothrombin fragment F1+2 and the clinical course in patients under intense anticoagulation after Palmaz Schatz coronary stenting.
Backgrounds. Monitoring of prothrombin fragment F1+2 (0.55-1.1 nmol/l) has been recommended to detect latent coagulation states and to prevent stent thrombosis by increasing heparin infusion at F1+2 values over 0.8 nmol/l. However, this strategy also also may increase the risk of bleeding complications.
Methods. To avoid the clinical course being influenced by information of the F1+2 results, daily F1+2 samples were deep frozen and analyzed after discharge. In 38 consecutive patients, 276 F1+2 samples (7.3 ± 2.1; range 4-10/patient) were analyzed.
Results. Mean F1+2 values under 0.55 nmol/l were not encountered. However, from stent implantation until discharge patients had therapeutic anticoagulation as determined by APTT and TT- measurements. One or more (3.4 ± 2.5; range 1-10, median 3) F1+2-values ≥1.1 nmol/l were found in 26 patients (68%). One of these patients (4%), with residual dissection between 2 stents, had stent thrombosis at day 9 (F1+2=1.3 nmol/l, APTT=90 seconds and TT=23%). Patients with a bleeding (n=11, samples=88, mean F1+2=1.10 ± 0.39 nmol/l) had higher mean F1+2- values, compared to patients without a bleeding (n=27, samples=188, mean F1+2=0.86 ± 0.37 nmol/l){p<0.0001}.
Conclusion. Since the incidence of stent thrombosis was low even at elevated F1+2- levels (4%), we do not recommend additional F1+2 monitoring after coronary stenting.

INTRODUCTION

Coronary stenting may play an important role in the prevention of restenosis after balloon angioplasty (PTCA) in native coronary arteries (1,2) or in venous bypass grafts (3) and in the treatment of suboptimal PTCA results (4,5,6). Part of the management after implantation of metallic stents consists of the treatment with a complex anticoagulant regimen, traditionally a combination of dextran, heparin, coumadin, acetosalicylic acid and dipyridamole, in order to prevent stent thrombosis (7,8). During adjustment on coumadin, patients are treated with heparin, titrated on Acitivated Partial Thromboplastin Times (APTT). Monitoring of prothrombin fragments F1+2 (normal range 0.55-1.1 nmol/l), released at the conversion of inactive prothrombin into active thrombin, has been recommended to detect impending subacute stent occlusion (9). Elevated F1+2- levels can be encountered, even in the presence of Activated Partial Thromboplastin Times (APTT) in a therapeutic range (10). In order to prevent subacute stent thrombosis, avoidance of dose reduction of heparin, even at therapeutic prothrombin time ratios (9) and additional heparinization at F1+2 levels > 0.8 nmol/l (11) or 1,2 microgr/l (12), has been advocated. Since puncture site related bleeding complications after coronary stenting in heparinized patients are frequently encountered, administration of extra heparin at therapeutic APTT's carries additional risk for bleeding complications. In this prospective study, the practical value of F1+2- assessments after coronary stenting is established by the relation between F1+2, APTT- and TT- values and the clinical course.
F1+2 samples were stored at -20°C and were analysed after discharge of the patient, in order to prevent the clinical course being influenced by knowledge of F12- values.

METHODS

Stent- implantation
All stent implantations were performed via the right femoral artery. The Palmaz Schatz stent was delivered with the stent delivery system, a preassembled unit, containing an articulated 15 mm, two segment stent, crimped on a specified diameter balloon and preloaded into a transparant sheath (13). Compared to the coronary artery diameter, the stented segment was slightly overdilated by repeat dilatations with a larger, non-compliant balloon.

Medical treatment
Pharmacologic treatment during the course of this study was aimed at the prevention of thrombosis and coronary spasm and consisted of the following:

Dextran 40, 100 cc/hour to a total of 1000 cc, starting 3 hours before stent implantation, or, in case of emergency stent implantation, from the moment the decision was made to implant a stent.

Heparin 10.000 IU was administered through the femoral artery sheath after its insertion, followed by 5.000 IU if the procedure lasted longer then 1 hour. Heparin infusion was discontinued immediately after stent implantation. The arterial sheath was removed when the Acticated Partial Tromboplastin Time (APTT) reached twice normal values (60-80 seconds). Two hours after hemostasis was achieved, a bolus of 5000 IU heparin was administered intravenously and heparin infusion was monitored with APTT measurements. When a vascular hemostasis device was applied, the arterial sheath was removed immediately after stent implantation and heparin was titrated to therapeutic APTT's, without discontinuation. Heparin infusion was gradually decreased over 24 hours when therapeutic adjustment on coumadin was obtained.

Acenocoumarol during 3 months: 6 mg the first day, 4 mg the second day, 2 mg the third day followed by a dosage adjusted to maintain a TT (Thrombotest [Nycomed, Pharmachemie, Haarlem, the Netherlands]) of 5 to 10%. Heparin was stopped when 3 consecutive TT's were in the therapeutic range. Additional medication consisted of **dipyridamole** 225 mg/day during 3 months, **acetylsalicylic acid** 300 mg/day during 6 months and **diltiazem** 180 mg/day for 1 month.

Monitoring of anticoagulation
Activated Partial Thromboplastin Time (APTT; normal 30-40 seconds)
APTT's were assessed every two hours after stent implantation to establish the optimal moment to remove the arterial introducer sheath (APTT=60-80 seconds). After readjustment on heparin, APTT was sampled 3 times a day, titrating heparin to APTT- values of 100 seconds. The mean of APTT- values from multiple samples in the course of one day during 10 days were calculated, to obtain an optimal reflection of the level of systemic heparinization.

Thrombotest [Nycomed] (TT; normal > 40%)
TT's were assessed once a day until patient discharge, when a stable adjustment on coumadin was established (TT ≤ 10%) during at least three consecutive measurements.

Prothrombin fragments F1+2 "Enzygnost® F1+2" (Behringwerke AG, Marburg, FRG) (F1+2; normal 0.55 - 1.1 nmol/l). Prothrombin fragment F1+2 samples were collected daily until patient discharge. Blood was drawn directly from a venous puncture and not from indwelling venous catheters. Plasma samples were obtained by centrifugation and stored deep frozen (minus 20^{o} Celcius) until analysis. Measurements were performed by enzyme immu-

noassay technique, according to the sandwich principle (14). F1+2 samples were tested at room-temperature according to the instructions accompanying the assessment kits.

Post procedural care
After sheath removal and manual compression or implantation of an vascular hemostasis device, a pressure dressing was applied overnight followed by 24 hours bed rest.

Statistical analysis
Mean values of APTT were calculated from all available samples of one day. Mean values of TT and F1+2 were calculated from single daily samples. Values were expressed as mean ± standard deviation. Means of F1+2 from patients with and without a bleeding complication were compared by Student's t-test. A probability value <0.05 was considered to be statistically significant.

RESULTS

Between april 1991 and november 1992, F1+2 monitoring was performed in 38 patients after successful implantation of Palmaz Schatz coronary stents.

Study population
Baseline clinical characteristics of the study population and indications for coronary stenting are summarized in Tables I and II, respectively. Distribution of stented vessels is illustrated in figure 1.

Table I. Baseline clinical characteristics.

Male	28 (74%)
Mean age (years)	60 ± 8 (42 - 76)
Risk factors	
Familiar	13 (34%)
Hypercholesterolaemia	13 (34%)
Smoking	11 (29%)
Hypertension	10 (26%)
Diabetes mellitus	6 (16%)
History	
Prior myocardial infarction	15 (39%)
Prior bypass surgery	12 (32%)
Prior PTCA	10 (26%)

PTCA= Percutaneous Transluminal Coronary Angioplasty

Table II. Indications for coronary stent implantation

De novo lesions in native coronary arteries	12 (32%)
Saphenous vein bypass graft stenosis	11 (29%)
Failed PTCA	10 (26%)
Restenosis	5 (13%)

PTCA= Percutaneous Transluminal Coronary Angioplasty

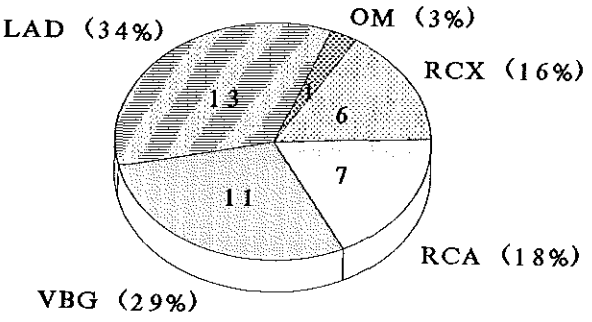


Figure 1. Distribution of stented target vessels

Clinical course

One patient (3%) developed subacute stent thrombosis. Bleeding complications, both access site related and systemic, were common in this population (n=11; 29%) {Table III}. Anticoagulation was not reversed in these patients. Four patients needed blood transfusions and 2 of them, also underwent vascular repair under anticoagulation (major bleeding; 11%).

Table III. Bleeding complications

	COMPLICATION	TRANSFUSION	SURGICAL REPAIR
1	Vaginal bleeding	No	No
2	Groin hematoma,	No	No
	AV- fistula		No
3	Groin hematoma	No	No
4	Brachial hematoma	No	No
5	Groin hematoma	Yes	Yes
6	Hematuria	Yes	No
7	Retroperitoneal bleeding,	Yes	No
	Nose bleeding	No	
8	Brachial hematoma	No	No
9	Femoral pseudo aneurysm	No	No
10	Femoral pseudo aneurysm,	No	No
	Hematuria		
11	Groin hematoma	Yes	Yes

Activated Partial Thromboplastin Times

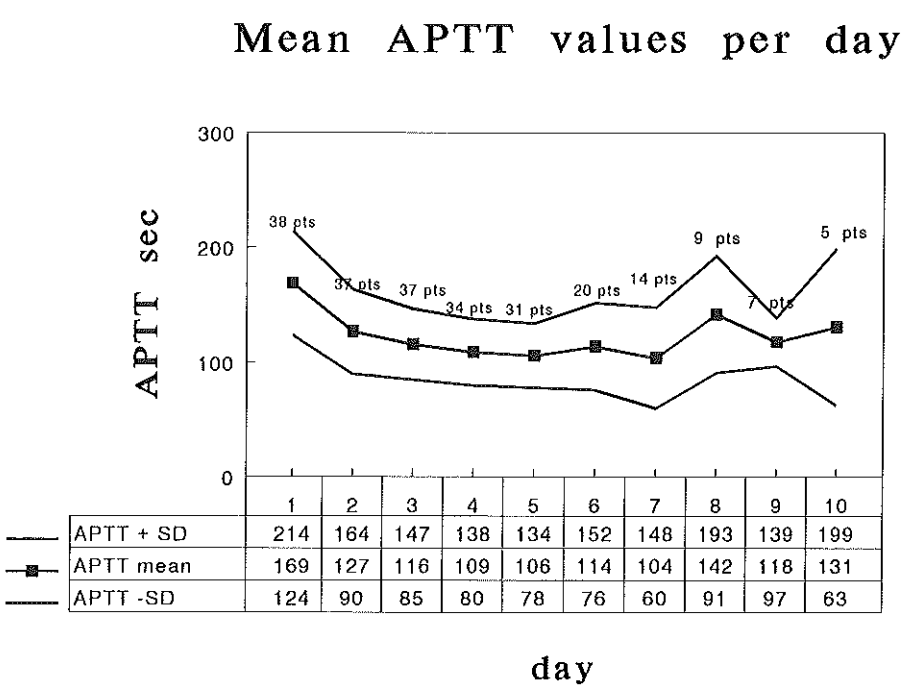
In figure 2, the course of mean APTT- values per day are given. The mean of all APTT- values was 124 ± 20 seconds. The maximum value was encountered at the day of stent implantation, reflecting therapeutic heparinization during the procedure and readjustment on heparin after removal of the arterial sheath. In the first week, APTT values could successfully be stabilized near a level of 100 seconds.

Thrombotests

The course of TT- values is shown in figure 3. At the fifth day following stent implantation, the mean TT reached therapeutic values.

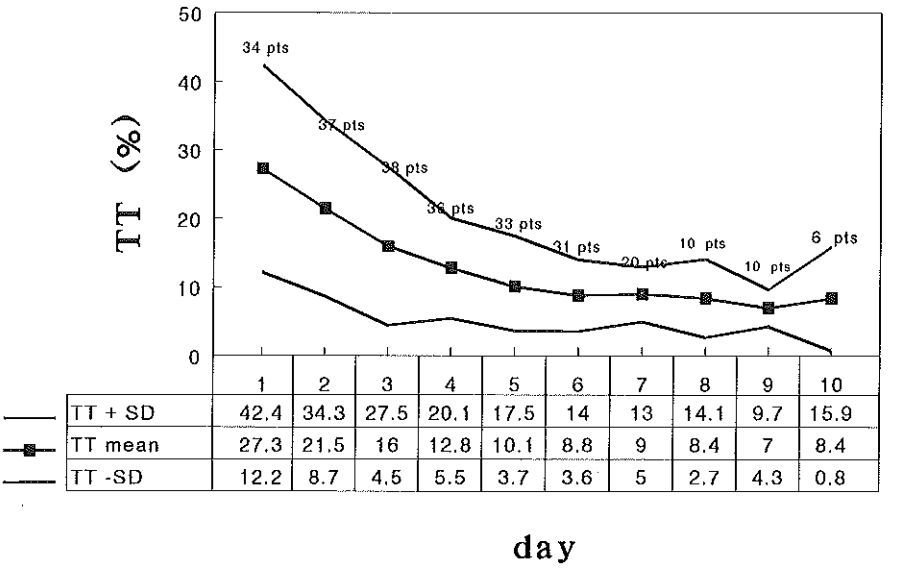
Prothrombin fragment F1+2

A total of 276 F1+2 samples were analyzed (7.3 ± 2.1 samples per patient; range 4-10).



	1	2	3	4	5	6	7	8	9	10
APTT + SD	214	164	147	138	134	152	148	193	139	199
APTT mean	169	127	116	109	106	114	104	142	118	131
APTT -SD	124	90	85	80	78	76	60	91	97	63

Figure 2. APTT values



	1	2	3	4	5	6	7	8	9	10
TT + SD	42.4	34.3	27.5	20.1	17.5	14	13	14.1	9.7	15.9
TT mean	27.3	21.5	16	12.8	10.1	8.8	9	8.4	7	8.4
TT -SD	12.2	8.7	4.5	5.5	3.7	3.6	5	2.7	4.3	0.8

Figure 3. TT- values

An overview of F1+2 values in the total study population is summarized in Table IV and the course of mean F1+2- values in the first 10 days is illustrated in figure 4.

Table IV. F1+2 values (nmol/l) for the total study population.

Day	N	Mean	Median	Range	SD
1	38	1.03	.91	.15-2.20	.52
2	38	.81	.74	.35-1.70	.35
3	37	.88	.84	.34-2.65	.43
4	38	.93	.85	.35-1.71	.34
5	34	.98	.97	.54-1.52	.30
6	31	.97	.93	.56-1.63	.33
7	23	1.06	.95	.47-2.00	.47
8	15	.91	.85	.42-1.65	.35
9	12	.92	.93	.42-1.95	.43
10	10	.77	.73	.30-1.30	.32

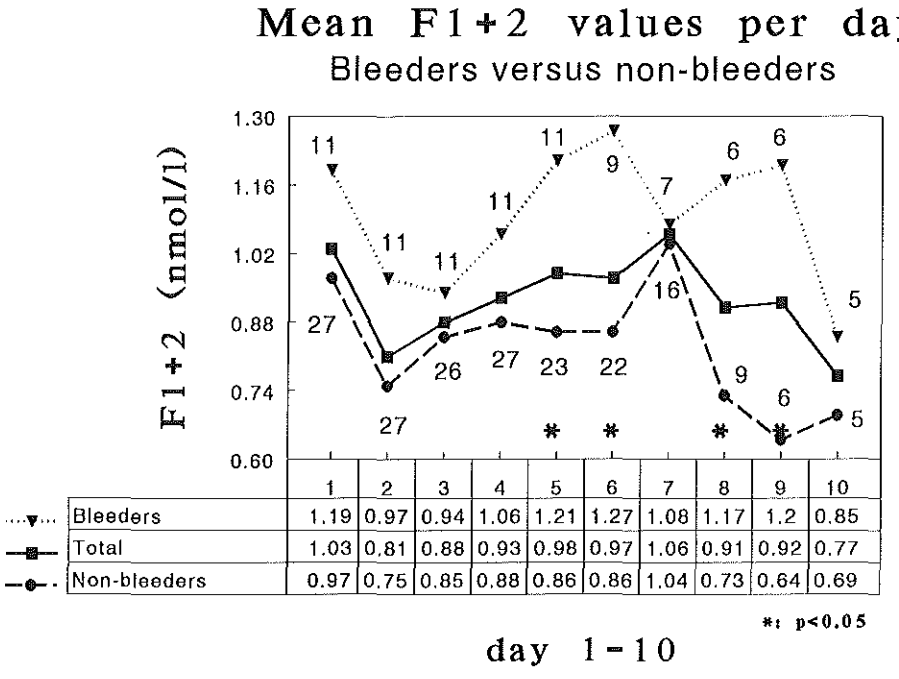


Figure 4. Mean F1+2 values for the total study population and for patients with and without a bleeding complication.

Mean F1+2 concentrations under 0.55 nmol/l were not found. In addition, one or more (3.4 ± 2.5; range 1-10, median 3) F1+2-values ≥1.1 nmol/l were found in 26 patients (68%). One of these patients, with a residual dissection between two stents, sustained subacute stent occlusion at day 10. At day 9 , heparin infusion was decreased at a TT of 8%. The TT at day 10 however was 23%, but the APTT was still within the therapeutic range (90 seconds). F1+2 rose from 0.65 to 1.3 nmol/l. When specified for patients with (n=11; #samples=88) and without (n=27; #samples= 188) a bleeding complication, the mean value of F1+2 was significantly higher in the first group (1.10 ± 0.39 nmol/l and 0.86 ±0.37 nmol/l respectively; p<0.0001)

(Table V and figure 4). In 5 of 11 patients with a bleeding complication (55%), the mean F1+2 values exceeded the upper normal value (1.1 nmol/l), whereas values in patients without a bleeding complication were within the normal range. In this group however, mean values did not fall under the lower normal value (0.55 nmol/l).

Table V. F1+2 values (nmol/l) for patients with and without bleeding complications.

	BLEEDING COMPLICATION				NO BLEEDING COMPLICATION				
Day	**N**	**Mean**	**Median**	**Range**	**SD**	**N**	**Mean**	**Median**	**Range**	**SD**
1	11	1.19	.95	.42-2.20	.66	27	.97	.90	.15-1.90	.40
2	11	.97	.85	.35-1.71	.44	27	.75	.73	.35-1.32	.29
3	11	.94	.95	.35-1.30	.32	26	.85	.73	.34-2.65	.47
4	11	1.06	1.10	.52-1.71	.33	27	.88	.82	.35-1.72	.33
5	11	1.21*	1.28	.70-1.52	.27	23	.86*	.81	.54-1.45	.25
6	9	1.27*	1.30	.69-1.60	.31	22	.86*	.78	.56-1.63	.26
7	7	1.08	1.10	.69-1.50	.31	16	1.04	.83	.47-2.00	.53
8	6	1.17*	1.08	.77-1.60	.32	9	.73*	.70	.42-1.10	.24
9	6	1.20*	.99	.90-1.95	.41	6	.64*	.65	.42-1.00	.21
10	5	.85	.75	.68-1.27	.24	5	.69	.70	.30-1.30	.40

* $p < 0.05$

DISCUSSION

Although suboptimal anticoagulation may be associated with increased risk for subacute stent thrombosis, optimal anticoagulation as measured by the APTT and TT, were not associated with a statisticallly significant reduced risk of stent thrombosis (15).
Daily measurements of prothrombin fragment F1+2 and coagulation factor II and subsequent adjustments of heparin infusion, has been advocated to reduce the incidence of subacute stent thrombosis. Haude et al demonstrated that monitoring of prothrombin fragment F1+2 could detect latent coagulation states after implantation of Palmaz Schatz stents (11). F1+2 levels over 0.8 nmol/l were associated with increased risk of subacute stent thrombosis. By giving extra heparin at elevated F1+2 values, even when APTT's were within the therapeutic range, stent thrombosis was retrospectively prevented in 39 patients of a consecutive group of 40 patients with F1+2 monitoring. In 53 patients without monitoring of F1+2, 9 subacute stent occlusions were reported.
Gulba et al reported that 8 of 34 patients showed increased F1+2 values, which normalized after extra heparinization (12). None of these patients suffered from stent occlusions.
Hafner et al. reported on 19 patients with F1+2 monitoring after Palmaz Schatz stent implantation (16). F1+2 levels were low (0.35 nmol/l) immediately after stenting and a rise was seen to 0.44 nmol/l in the first and second day. After a second peak to 0.44 nmol/l at day 6, a continous decrease was observed to 0.29 nmol/l. None of the patients developed stent thrombosis. By analyzing daily collected F1+2 samples after discharge of patients with coronary stents and thus by refraining from intervention in the anticoagulation regimen, we were able to correlate the clinical outcome with F1+2 concentrations. Only one patient from the 26 patients with F1+2 levels above the normal value, who had a suboptimal stent result, developed subacute stent occlusion. In a study of Strumpf et al. F1+2 was measured in 37 consecutive patients after elective stent implantation (17). Five of these patients developed stent thrombosis. F1+2 levels for patients with thrombosis did not significantly differ from patients without this complication; 1.046 ± 0.156 ugr/l and 1.009 ± 0.217 ugr/l respectively. The natural course

of patients with increased F1+2- levels remained unknown in the studies of Haude (11), Gulba (12) and Hafner (16), because these patients received extra heparin.
Surprisingly, in our study mean F1+2 values were higher then the recommended 0.8 nmol/l. This discrepancy in F1+2 levels can not be explained by a difference in anticoagulant therapy, although in the study of Hafner et al (16) heparin is continued after angioplasty at an infusion rate of 1000-1800 IU/h. According to our protocol heparin is discontinued untill the introducer sheath can be removed after at an APTT at 60 seconds, 2 hours later followed by readjustment on heparin. Before and during readjustment, episodes of suboptimal anticoagulation were observed in individual patients. However, during heparinization, our patients were under adequate anticoagulation as indicated by the APTT- values. Blood sampling and laboratory assessment were performed strictly according to instructions from the manufacurer (Enzygnost F1+2, Behring, Marburg, France). A theoretical explanation for the elevated F1+2- levels may be in vitro generation of F1+2 in stored plasma samples at low temperatures. Since we did not perform control analyses of F1+2 from fresh plasma and stored plasma from the same patient, this question will remain unresolved in this patient group.
The higher F1+2 levels in patients with clinical evidence of bleeding, can be explained by the fact that any bleeding will be associated with activation of hemostatic processes.
This hypothesis also explains the paradox of effective anticoagulation (therapeutic APTT from day 1-10 and TT from day 5-10) and bleeding complications on one hand, and hypercoagulability, represented by increased F1+2 levels on the other hand.
Since activation of hemostatic processes by bleeding cannot be differentiated by means of F1+2- monitoring from impending stent occlusion, we do not perform F1+2-monitoring as a routine after Palmaz Schatz stent implantation and we consider APTT and TT- values adequate parameters to monitor anticoagulant therapy following this intervention.

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CHAPTER 4.3

POTENTIAL SOLUTIONS

IMPROVEMENT OF LOCAL HEMOSTASIS

IMPROVED ANTICOAGULATION MANAGEMENT AFTER PALMAZ SCHATZ CORONARY STENT IMPLANTATION BY SEALING THE ARTERIAL PUNCTURE SITE WITH A VASCULAR HEMOSTASIS DEVICE

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Improved Anticoagulation Management After Palmaz Schatz Coronary Stent Implantation by Sealing the Arterial Puncture Site With a Vascular Hemostasis Device

Ferdinand Klemenelj, MD, and
Gert Jan Laarman, MD, PhD

Sealing the arterial puncture site with a vascular hemostasis device has the potential to maintain optimal anticoagulation after stent implantation. The level of heparinization during the first 3 days after successful stent implantation was retrospectively compared between 2 groups of medically treated patients with (group A; n = 18) and without (group B; n = 17) a Vasoseal™ after sheath removal. The number of APTTs sampled in group A and B was 233 and 168, respectively. Respective mean values of APTT (seconds) in group A and B were 180 ± 79 and 172 ± 91 at day 1 (p = NS), 132 ± 43 and 125 ± 61 at day 2 (p = NS) and 123 ± 36 and 116 ± 48 at day 3 (p = NS). More APTTs were suboptimal (< 80 secs) in group B (34/168; 20%) compared to group A (17/233; 7%) [p < 0.001]. More patients in group B compared to group A had 1 or more (14/17; 82% vs. 8/18; 44%; p = 0.04), 2 or more (10/17; 59% versus 3/18; 17%; p = 0.02) and 3 or more (8/17; 47% vs. 2/18; 11%; p = 0.03) suboptimal APTTs. Bleeding complications were seen in 4 patients without and in 3 patients with a Vasoseal™. Thus application of a vascular hemostasis device results in a less variable anticoagulation after coronary stenting, but it does not abolish entry site-related bleeding complications. © 1993 Wiley-Liss, Inc.

Key words: coronary stent, biodegradable collagen hemostasis device

INTRODUCTION

After removal of the arterial introducer sheath in patients undergoing implantation of a metallic coronary stent, a careful balance between anticoagulation and hemostasis has to be maintained. Usually, immediately after stent implantation, heparin is temporarily discontinued. When Activated Partial Thromboplastin Times (APTT) reaches twice the normal value (80 secs), the sheath is withdrawn. Readjustment on heparine is started several hours after local hemostasis is achieved by giving a bolus intravenously resulting in a peak in the APTT curve, followed by continuous heparin infusion. APTTs are maintained at a stable level near 100 secs, until effective adjustment on coumarin is established (Fig. 1). In a clinical setting, however, monitoring and adjustment of anticoagulation can be less optimal. Episodes of subtherapeutic anticoagulation can occur not only during the initial discontinuation of heparin, but also during the readjustment phase, as there are inevitible time lapses between blood sampling, laboratory assessment, and the final announcement of the APTT result.

These episodes of suboptimal anticoagulation may subject the patient to an increased risk of stent thrombosis. Recently, local application of a collagen containing vascular hemostasis device (Vasoseal™) has been proposed for a selected group of patients, as an alternative to prolonged femoral compression after sheath removal [1]. After insertion of such a device, heparin can be smoothly titrated to APTT levels near 100 secs, obviating early suboptimal heparinization and a fluctuating heparin readjustment-phase. In this retrospective study we report on our experience with this new device in relation to the quality of heparinization.

METHODS

Study Population

The study group was derived from medically treated patients after successful stent implantation during the same period of stent experience, and after either successful implantation of a vascular hemostasis device (group A) or after conventional sheath removal with prolonged local pressure application (group B).

Stent Implantation

The stent delivery system was used: a sheath protected unit, containing the articulated Palmaz Schatz stent, crimped on a specified diameter balloon catheter. Compared to the coronary artery diameter, the stented segment was slightly overdilated by repeat dilatations with a larger, noncompliant balloon.

Insertion of a Vascular Hemostasis Device

Percutaneous entry of the femoral artery was attempted under an angle of 45–60°. With the appearance of pulsatile blood from the needle, a clamp was placed at the needle at skin level to mark the distance between the skin and arterial wall. The needle was withdrawn and

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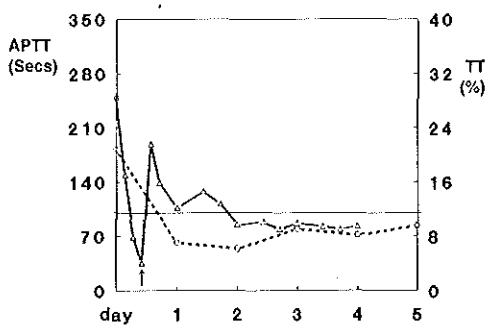

Fig. 1. Ideal Activated Partial Thromboplastin Time (APTT) and Thrombotest (TT) curves following arterial sheath removal. APTT falls under 80 secs (arrow) before the sheath is removed from the femoral artery. After 2 hr the patient is heparinized, giving rise to a peak in the APTT curve, followed by stabilization around 100 secs.

placed on the Vasoseal™ color card. The color at the needle tip corresponds to a Vasoseal™ kit of the same color, containing 2 collagen plugs of a length determined by the arterial depth measurement.

The arterial sheath was removed over a guidewire under occlusive compression 3–4 cm above the puncture site. A blunt tissue dilator was advanced to a black marker line or untill resistance is felt. The Vasoseal™ sheath was advanced over this dilator until the proximal opening was aligned with the colored band on the dilator. Tissue dilator and guidewire were removed and the first collagen cartridge was inserted followed by delivery of the plug by advancing the plunger. After waiting 3–5 secs, the plunger was removed and a second plug was inserted, followed by withdrawal of the sheath. Local pressure was applied for 5 min after collagen insertion, followed by application of a pressure dressing.

Exclusion criteria for Vasoseal™ application were absence or abundance of subcutaneous tissue, presence of a hematoma, no previous arterial depth measurement, uncontrolled hypertension and known allergy to collagen or beef products. Both investigators had applied this technique routinely in patients after coronary artery balloon angioplasty, before using this device in patients after coronary stenting.

Medical Treatment

Pharmacologic treatment was aimed at the prevention of thrombosis and spasm and consists of the following: Rheomacrodex 40, 100 cc/hr to a total of 1 litre, started 2 hr before the procedure or from the moment the decision was made to implant a stent after failed PTCA. Heparin 10,000 IU was administered through the femoral artery sheath after its insertion, followed by 5,000 IU for each hr during the procedure. When no Vasoseal™ was applied, the arterial sheath was removed when the Activated Partial Tromboplastin Time (APTT) reached twice normal values (80 secs). Two hr after obtaining local hemostasis, a bolus of 5,000 IU heparin was administered intravenously and a heparin infusion was titrated to APTT's near 100 secs, measured with 8-hr intervals or more frequent if necessary. When a vascular hemostasis device was applied, the arterial sheath was removed immediately after stent implantation and heparin was titrated to APTTs of 100 secs, without discontinuation. Acenocoumarol during 3 mos: 6 mg the first day, 4 mg the second day, 2 mg the third day followed by a dosage adjusted to maintain a TT (thrombo-test "QUICK") of 5–10%. Heparin was stopped when 3 consecutive TTs were in the therapeutic range. Additional medication consisted of dipyridamole 225 mg/day during 3 mos, acetylsalicylic acid 300 mg/day during 3 mos, and diltiazem 180 mg/day for 3 mos.

Postprocedural Care

After sheath removal and manual compression of the groin or implantation of an vascular hemostasis device, a pressure dressing was applied overnight followed by an 24-hr immobilization period.

Statistical Analysis

Statistical analysis was performed with a commercially available software program. Results are reported as mean value ± 1x standard deviation (SD).

The number of total APTTs and suboptimal APTTs in group A and B were compared by the Chi-square test. Baseline clinical characteristics and patients with more then 1, 2, and 3 suboptimal APTTs in both groups was compared by the Fisher's exact test. Differences in mean APTTs were compared by the Student's t-test. A p value < 0.05 was considered significant.

RESULTS

Baseline Clinical Characteristics

Between May 1991 and May 1992, 36 consecutive patients were medically treated after successful coronary stent implantation.

One patient with a Vasoseal had an ischemic cerebrovascular accident the day of stent implantation. She developed a major puncture-site bleeding, caused by confusion and extreme restlessness. Because heparin had to be discontinued for a prolonged period of time until a hemorrhagic stroke was excluded by computerized tomography, analysis of anticoagulation could not be included in this study. Consequently, 35 patients were

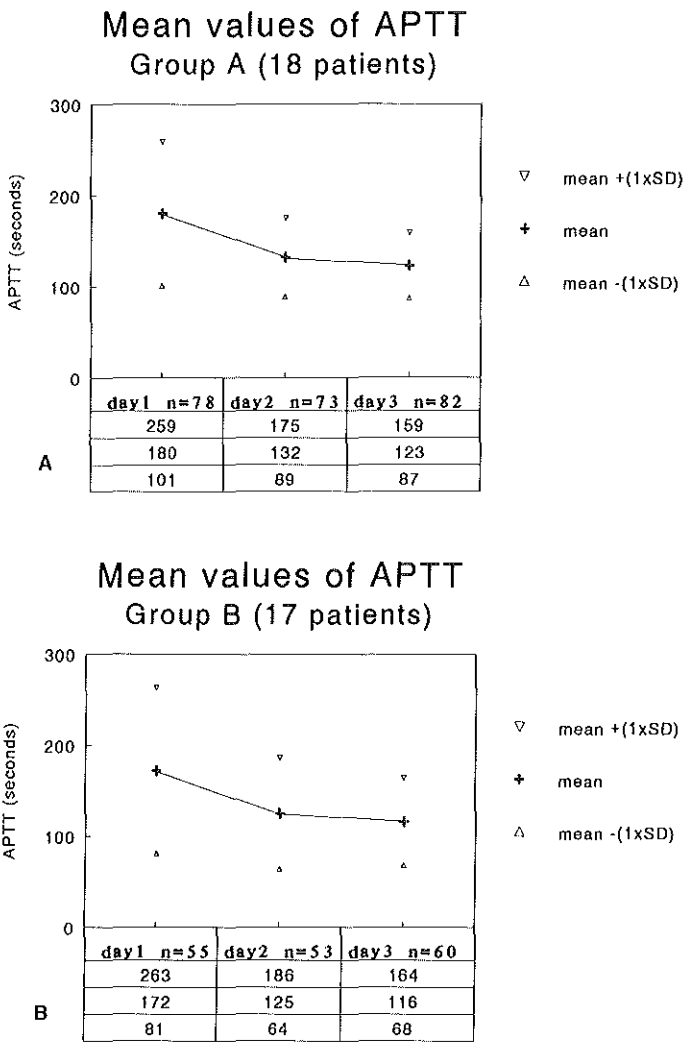

Fig. 2. A. Level of APTTs in group A during the first 72 hr after stent implantation (mean ± 1 SD). B. Level of APTTs in group B during the first 72 hr after stent implantation (mean ± 1 SD).

compared, 18 patients with (group A) and 17 patients without (group B) a Vasoseal®.

Baseline clinical characteristics are summarized in Table I.

In group A, more patients underwent elective stent implantation (61%) and venous bypass graft stenting (33%) compared to group B (47% and 6%, respectively). This difference is explained by the fact that skin-femoral artery distance measurements for determination of the plug length were routinely performed prior to sheath insertion in all elective and saphenous vene graft stenting procedures but not in all PTCA procedures leading to emergency stenting. Ignorance of plug length was considered to be a contraindication for arterial sealing.

TABLE I. Baseline Clinical Characteristics of Patients Treated With (group A) and Without a Vascular Hemostasis Device (group B)

	Group A (n = 18)	Group B (n = 17)	P*
Male	14	15	NS
Age (yr)	59 ± 8	57 ± 8	NS
Procedure			
Elective	11 61%	8 47%	NS
Bailout	7 39%	9 53%	NS
Vessel[a]			
LAD	6 33%	9 53%	NS
LCX	5 28%	2 12%	NS
RCA	1 6%	5 29%	NS
VBG	6 33%	1 6%	NS

[a]LAD-left anterior descending coronary artery; LCX-left circumflex coronary artery; RCA-right coronary artery; VBG-venous bypass graft.
*Fisher exact test.

TABLE II. Level of Anticoagulation in Patients With (group A) and Without (group B) a Vascular Hemostasis Device

	Group A (n = 18)	Group B (n = 17)	P
APTT[a] day 0–3	233	168	
APTT (<80 sec)	17/233 (7%)	34/168 (20%)	<0.001*
≥1 APTT (<80 sec)	8/18 (44%)	14/17 (82%)	0.04**
≥2 APTT (<80 sec)	3/18 (17%)	10/17 (59%)	0.02**
≥3 APTT (<80 sec)	2/18 (11%)	8/17 (47%)	0.03**

[a]Activated partial thromboplastin time.
*Chi-square test.
**Fisher exact test.

Level of Anticoagulation

A suboptimal APTT was defined as a value under 80 secs, twice the upper value of the normal range. In the first 72 hr after stent implantation, the number of APTTs sampled in group A and B was 233 and 168, respectively (Table II). Mean values of APTTs (secs) in group A and B are illustrated in Figure 2a,b. Although the level of APTTs at day 1,2, and 3 was higher in group A compared to group B, the differences were not statistically significant. More APTTs were suboptimal (< 80 seconds) in group B (34/168; 20%) compared to group A (17/233; 7%) [$p < 0.001$]. More patients in group B compared to group A had 1 or more (14/17; 82% vs. 8/18; 44%), 2 or more (10/17; 59% vs. 3/18; 17%) and 3 or more (8/17; 47% vs. 2/18; 11%) suboptimal APTTs.

Complications

Four patients without a hemostasis device had bleeding complications, three related to the puncture site. All puncture-site-related complications in this group were arteriovenous fistulas. One patient also had macroscopic hematuria in the presence of a renal cyst. Another patient had macroscopic hematuria requiring blood transfusion. Surgical correction was necessary for one patient with an AV fistula.

One patient with a Vasoseal underwent vascular surgery for a femoral artery pseudoaneurysm after a groin bleeding following an ischemic cerebrovascular accident as outlined above. Another patient developed puncture-site bleeding immediately following insertion of a Vaseseal. This patient required blood transfusions and acute vascular surgery.

The third complication after arterial sealing was encountered in a patient who developed a spontaneous groin bleeding 2 days after stent implantation. Two mos later, the organized hematoma was surgically removed, because of femoral nerve compression. Subacute stent thrombosis occurred in one patient without a hemostasis device, at the third day after stent implantation, successfully recanalized by rePTCA and subsequent coronary bypass surgery. This patient had 2 subtherapeutic APTT values before stent occlusion occurred.

DISCUSSION

Coronary stent implantation has been proposed as a possible solution for 2 major limitations of conventional balloon angioplasty; abrupt closure during or late after the procedure [2–7] and late restenosis in native coronary arteries [8,9] and saphenous vein grafts [10]. However, subacute stent thrombosis after implantation of a Palmaz Schatz balloon expandable coronary stent has been reported to occur in 0.4% of 220 pts after both elective and bailout stent implantation [11] to 25% of patients after emergency stent implantation for failed PTCA during early experience [7]. Risk factors for subacute stent thrombosis include: stenting for suboptimal PTCA, vessel size smaller than 3.25 mm, multiple stent implantation, poor LVEF [12], residual dissection [13], intracoronary thrombus [14], and suboptimal anticoagulation [8].

Implantation of metallic coronary stents requires intense anticoagulation, which usually consists of a combination of Dextran, dipyridamole, acetosalicylic acid, and heparin [15]. Of 39 patients in the multicenter study from Schatz et al. [8], anticoagulated without coumarin, 7 patients suffered from stent thrombosis. Subacute thrombosis decreased significantly from 18% to 0.6% in those patients who also received coumarin.

This aggressive anticoagulation regimen is associated with a high incidence of puncture-site-related bleeding complications, reported to vary between 7.9% of 226 patients in the initial multicenter experience with the Palmaz Schatz stent [8] and 16% of 220 patients in the

single center experience of Carrozza et al. [11]. A bleeding complication after stent implantation is a serious event, because this disturbes the anticoagulation regimen and subsequent risk for stent thrombosis. In order to prevent local bleeding complications, the arterial sheath is removed within 24 hr after stent implantation under a low level of heparinization and preferably not during continued anticoagulation with heparin and coumarin. When the patient is subsequently readjusted on heparin, several short episodes of undercoagulation may still occur. These episodes of suboptimal heparinization can be prevented by immediate postprocedural sealing of the arterial puncture site, obviating the need for early discontinuation of heparin and allowing titration of APTTs to values near 100 secs. This study was performed to evaluate the quality of heparinization in patients treated with a vascular hemostasis device after coronary stent implantation. The device used in our study was the biodegradable, collagen-containing, supraarterial plug (Vasoseal®), recommended as an alternative for prolonged local pressure application [1,16].

Although the level of heparinization, as determined by the mean of APTT- values in the first 72 hr, did not differ significantly in both groups, less APTTs were in the subtherapeutic range in patients with a Vasoseal, signifying an optimized adjustment on heparin. The clinical relevance of adequate heparinization immediately after arterial sealing, however, remains theoretical at this time. Although stent occlusion within the first 24 hr is a rare phenomenon [12], early episodes of suboptimal heparinization may theoretically form the nidus for future subacute stent thrombosis. In contrast, postponing readjustment on heparin for 6 hr after removal of the arterial sheath has presently been recommended in order to prevent vascular complications. Since no studies are performed, evaluating the optimal heparinization regimen postcoronary stenting, our policy to strive for therapeutic heparinization as soon as possible after stent implantation and local hemostasis is legitimate.

The role of vascular hemostasis devices in preventing local bleeding complications also remains a matter of debate. The small number of patients and the nonrandomized character of this study, where no corrections for baseline factors such as body size, hypertension, elective vs. emergency stenting, were made, does not allow any conclusion concerning the differences in clinical endpoints such as bleeding and cardiac complications. Only a difference in laboratory values was found. In our experience, despite careful patient selection and optimal insertion and immobilization techniques, serious groin bleeding could not be abolished in 3 patients after application of a Vasoseal. In a randomized study comparing sheath removal and manual compression vs. insertion of a Vasoseal in 60 patients after PTCA, Camenzind e.a. did not find a significant reduction in bleeding complications [17].

However, techniques of coronary stenting and postprocedural policies are dynamically evolving. Efforts are directed toward the development of nonthrombogenic stents, downsizing of PTCA equipment, allowing smaller vascular puncture holes [18], alternative entry sites such as the radial artery [19] for stent implantation, improvement of local femoral pressure application by an inflatable compression device [20], and several vascular hemostasis devices [21].

In order to determine the optimal strategy after implantation of the current Palmaz Schatz stent, aiming at a reduction of subacute stent thrombosis *and* of puncture-site bleeding complications, several studies need to be designed comparing these and future strategies in a randomized fashion.

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CHAPTER 4.4.1

POTENTIAL SOLUTIONS

RADIAL ARTERY AS ENTRY SITE

Feasibility of bailout techniques with 6 French guiding catheters

FIRST CLINICAL EXPERIENCE WITH A NEW LOW PROFILE CORONARY PERFUSION BALLOON CATHETER COMBINED WITH 6 FRENCH GUIDING CATHETERS

F. Kiemeneij, G.J. Laarman

J Invas Cardiol 1993;5:219-224

First Clinical Experience With a New Low Profile Coronary Perfusion Balloon Catheter Combined With 6 French Guiding Catheters

Ferdinand Kiemeneij, MD and Gert Jan Laarman, MD, PhD

ABSTRACT: At present, the use of 6 French (F) guiding catheters is limited by the inability to accommodate large catheter systems, such as perfusion balloons, stent delivery systems and catheters for intravascular ultrasound. In this study the performance of a new, low profile perfusion balloon catheter, in combination with 6F guiding catheters, was evaluated in 12 consecutive patients undergoing coronary angioplasty (PTCA). In all patients the ACS® Flowtrack™40 perfusion catheter, used as a primary device, was successfully advanced towards and retrieved from the coronary artery. However, repositioning of the perfusion catheter was not possible in all cases. In 10 patients (83%) the catheter could be positioned across the coronary artery stenosis. Distal contrast opacification during balloon inflation was present in all these instances. Severe anginal complaints, necessitating extra antianginal treatment or cessation of balloon inflation and hemodynamic deterioration did not occur during inflations of 270 ± 136 seconds (range 105-480; median 300). PTCA was successful in all patients. Diameter stenosis was reduced from 67 ± 10% (range 42-79%) to 23 ± 12% (range 2-40%) and minimal luminal diameter increased from 0.8 ± 0.3 mm (range 0.4-1.4 mm) to 2.2 ± 0.6 mm (range 1.4-3.0 mm). The clinical course was uneventful in all patients. These results demonstrate that this promising perfusion catheter further reduces the limitations of 6F guiding catheters. However, there is still need for improvement in the performance of this device.

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Key words: PTCA, perfusion balloon catheter, 6 French guiding catheter

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New 6 French (F) guiding catheters for coronary angioplasty can accommodate low profile, rapid exchange balloon catheters.[1,2] Advantages of small sized guiding catheters are the ability to perform procedures with smaller arterial puncture holes, with the potential of less bleeding complications

Table 1. Crossing profiles for different balloon sizes

Balloon size (mm)	2.0	2.5	3.0	3.5	4.0
Crossing profile					
-inch	.048	.049	.050	.051	0.52
-mm	1.22	1.24	1.27	1.30	1.32

and early ambulation, the use of smaller arterial entry sites, such as the brachial[3] and radial arteries[2] and less pressure damping by the guiding catheter in the coronary ostium. Performance of 6F guiding catheters with regard to contrast delivery, pressure monitoring and backup support is similar to 8 F guiding catheters.[4] However, a potential limitation of the use of 6F guiding catheters is the inability to accommodate large catheter systems, such as perfusion balloons, atherectomy catheters, stent delivery systems and catheters for intravascular ultrasound. To evaluate the performance of a new, low profile, perfusion balloon catheter in combination with 6F guiding catheters, we selected this catheter as a primary device in 12 consecutive patients undergoing coronary angioplasty (PTCA).

MATERIALS AND METHODS

Patient selection. Twelve consecutive patients, undergoing elective coronary balloon angioplasty were included after having given informed consent.

Guiding catheter. For this study, Scimed® 6F Triguide–Elite™ guiding catheters were used. These catheters are 100 cm long and have an inner diameter of 0.060 inch (1.53 mm).

Perfusion balloon catheter. The perfusion balloon catheter used was the ACS® RX Flowtrack™40 (Figure 1). Flow rate of this perfusion balloon is 40 cc/min. This rapid exchange (20 cm "peel–away") catheter consists of a 135 cm long Dynacross™ shaft (proximal 2.3F and distal 3.5F). The shaft has 14 perfusion holes, 0.014 inch in diameter, 10 proximal and 4 distal from the balloon. The balloon is made of PE-600. Rated burst pressure is 8 atmospheres. The distal 30 cm of this device is coated with Microglide™. Crossing profiles for different balloon sizes are summarized in Table 1.

Medical treatment. Through the arterial introducer sheath, 10,000 IU heparin was administered. Prior to contrast injection (Hexabrix® 320), nitroglycerin 100-200 micrograms was given intracoronary. For severe angina, intracoronary administration of nitroglycerin was repeated or nifedipine 10 mg was administered sublingually. A combination of fentanyl 0.05 mg and droperidol 0.25 mg (Thalamonal®) 1-2 ml intravenously was given for refractory anginal complaints.

Angioplasty. After crossing the obstructing coronary lesion, the balloon was inflated to 6-8 atmospheres. Presence of distal flow, defined as distal contrast opacification of the coronary artery during balloon inflation and the contrast agent disappearing after a few cardiac cycles, was angiographically assessed. The guiding catheter and guidewire were subsequently withdrawn towards the shaft marker in order to maximize

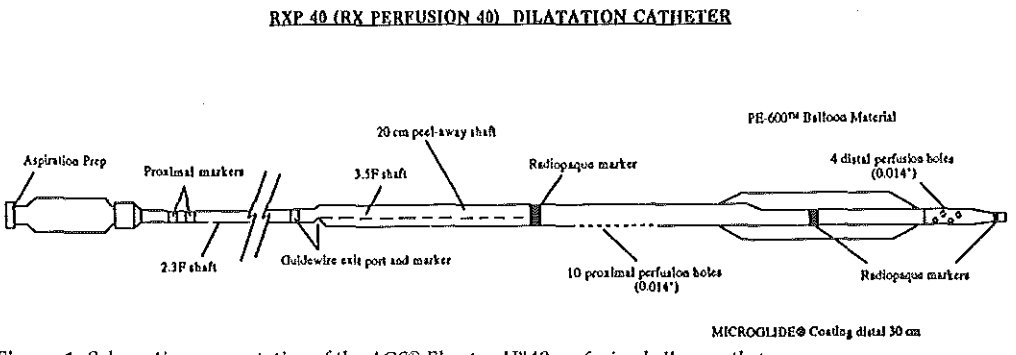

Figure 1. *Schematic representation of the ACS® Flowtrack™40 perfusion balloon catheter.*

Table 2. Baseline clinical characteristics (N=12)

	N	
Male	11	(92%)
Age (mean ± SD)	58.3 ± 8.6 years	
Angina		
Exertional	11	(92%)
CCS I	0	
CCS II	2	(17%)
CCS III	7	(58%)
CCS IV	2	(17%)
Non Exertional	2	(17%)
Mixed	1	(8%)
Previous MI	7	(58%)
Previous CABG	1	(8%)
Previous PTCA	4	(33%)
Diabetes mellitus	1	(8%)
Hypertension	3	(25%)
Hypercholesterolemia	1	(8%)
Familiar	2	(17%)
Smoker	9	(75%)

CCS = Canadian Cardiovascular Society;
M I= myocardial infarction;
CABG = coronary artery bypass grafting;
PTCA = percutaneous transluminal coronary angioplasty

perfusion.

Recording of events and performance of angioplasty equipment. Onset and severity of chest pain, hemodynamic deterioration (drop of blood pressure ≥ 20 mmHg) and EKG changes were recorded, as well as the treatment required. Performance of the guiding catheter (backup support and opacification) and of the perfusion catheter (crossability and retrievability) were semiquantitatively scored in 3 categories; good, moderate (sufficient; no need to change guiding or balloon catheter) and poor (suboptimal; need to change guiding or balloon catheter). Pre– and post–PTCA angiographic studies were performed with a computerized quantitative coronary analysis system (DCI, Philips Medical Systems).

RESULTS

Study population (Table 2). Twelve patients underwent PTCA with a Flowtrack 40 perfusion balloon as the primary device. Baseline clinical characteristics and demographics are summarized in Table 2.

Angiographical data (Table 3). Thirteen lesions were attempted in 12 coronary arteries.

Table 3. Angiographical data

	N	
Vessels	12	
Culprit lesion	13	
LAD	4	(31%)
RCA	7	(53%)
RCX	1	(8%)
AL	1	(8%)
Flow (TIMI)		
3	12	(100%)
Type		
A	5	(39%)
B	6	(46%)
C	2	(15%)

Quantitative angiography

	Mean ± SD	Range
Reference diameter	2.6 ± 0.8 mm	1.3 - 3.9 mm
Minimal luminal diameter	0.8 ± 0.3 mm	0.4 - 1.4 mm
Diameter stenosis	67 ± 10%	42 - 79%

LAD = Left anterior descending coronary artery
RCA = Right coronary artery
LCX = Left circumflex coronary artery
AL = Anterolateral branch

Entry sites and guiding catheter selection. Entry sites for PTCA were the femoral (n=8; 67%), radial (n=3; 25%) and brachial (n=1; 8%) arteries. Guiding catheter curves selected were FR4 (n=5), FL4 (n=4), FR 3.5 (n=1), El Gamal (n=1) and Voda (n=1). Cannulation of the coronary artery was successful in all patients. Opacification of the coronary artery and pressure monitoring was good in all patients. Backup support was good in 10 patients and moderate in 2 patients.

Dilatation catheters

Number: Fourteen Flowtrack 40 catheters were used (2.5 mm; n=5: 3.0 mm; n=6: 3.5 mm; n=3). A second (3 patients) or third (2 patients) balloon catheter was required to further optimize the result.

Crossing, retrieval and repositioning: (Patients; n=12, Flowtrack 40; n=14) Ability of the Flowtrack 40 to cross the stenosis was considered good in 8 (58%), moderate in 2 (21%) and poor in

2 (21%) instances. In one patient a Flowtrack 40 2.5 mm could not cross a small anterolateral branch stenosis (RD 1.3, MLD 0.4 mm). The other patient had a 20 mm long stenosis in the right coronary artery (RD 2.2, MLD 0.8 mm), which could not be crossed by a 2.5 mm perfusion balloon. These patients had successful PTCA with a Scimed® Express™ balloon catheter. Eleven perfusion balloon catheters could be retrieved from the guiding catheter without noticeable friction (79%), while some friction was felt in 3 patients (21%). In 5 patients repositioning of the balloon was attempted, to optimize the angioplasty result. In 3 patients it was impossible to recross the shaft of the guiding catheter after complete retrieval. All failed attempts were due to lack of stiffness of the distal shaft at the site of the peel-away slit. The lesions were successfully recrossed with Scimed Express balloon catheters. In the remaining 2 patients, repositioning the balloon in the coronary artery was successful, after partial retrieval of the perfusion balloon to just proximal of the dilated segment.

Balloon inflation and clinical tolerance: (Patients; n=10, Flowtrack 40; n=12) Mean duration of perfusion balloon inflation was 270 ± 136 seconds (range 105-480; median 300). Distal perfusion during balloon inflation could angiographically be demonstrated in all these patients. One patient (10%) had clear, but acceptable, anginal complaints. Seven patients (70%) had mild angina during inflation. Of the patients with angina, two had associated 1 mm ST-segment elevation and three had 1 mm ST-segment depression. Extra anti-anginal treatment was not given. No significant blood pressure drop during balloon inflation was recorded.

Angiographical and clinical results. (Patients; n=12) PTCA was successful in all patients. Diameter stenosis was reduced from 67 ± 10% (range 42-79%) to 23 ± 12% (range 2-40%); RD from 2.6 ± 0.8 (range 1.3-3.9 mm) to 2.8 ± 0.7 mm (range 1.7-4.2 mm); MLD from 0.8 ± 0.3 mm (range 0.4-1.4 mm) to 2.2 ± 0.6 mm (range 1.4-3.0 mm). In three patients (25%) a small dissection (staining of some contrast medium parallel to the vessel wall, vanishing after a few cardiac cycles) was noted. No other angiographic complications were encountered. Clinical course was uneventful in all patients.

DISCUSSION

Since the introduction of PTCA for treatment of coronary artery disease, angioplasty equipment has been miniaturized. Low profile balloon catheters can now be used in association with 6F guiding catheters.[1,2] and in selected cases even with 4F diagnostic catheters.[5] The major advantage is the smaller arterial puncture hole, a key factor in preventing post procedural vascular complications. Another advantage is the possibility of selecting smaller arteries as entry sites, such as the brachial artery[3] and radial artery,[2] in order to reduce incidence and severity of vascular complications. Backup support and vessel opacification of 6F guiding catheters are comparable with 8F guiding catheters.[4] However, one of the limitations of 6F guiding catheters is that they do not allow larger catheter systems, such as perfusion balloons, stent delivery systems, atherectomy catheters and catheters for intravascular ultrasound.

Perfusion balloons may be useful as primary tools if myocardial protection during inflation is required,[6] for example, if the patient does not tolerate inflations of normal duration because of severe angina or if hemodynamically dependent on the angioplasty vessel.[7] Prolonged dilatations may be required to improve acute suboptimal PTCA results[8] or to stabilize the patient before emergency coronary bypass surgery after failed PTCA, if stent implantation is impossible or contraindicated.[9] The currently available perfusion balloons can only be used in combination with large bore guiding catheters.

As demonstrated in this study, the low profile ACS Flowtrack 40 perfusion balloon catheter can be used in combination with 6F guiding catheters, allowing distal perfusion during balloon inflation (Figures 2A, B and C). Only recrossing the perfusion catheter after complete retrieval from the guiding catheter turned out to be cumbersome or sometimes even impossible in some instances. To overcome friction between the perfusion catheter, now with a larger profile after initial inflations, and the guiding catheter, a considerable forward pushing force is applied at the proximal hypotube catheter shaft. The flexible and relative weak part of the distal shaft, containing the peel away slit, easily kinks under these circumstances, resulting in prolapse of the guidewire through this slit. To overcome friction between the guid-

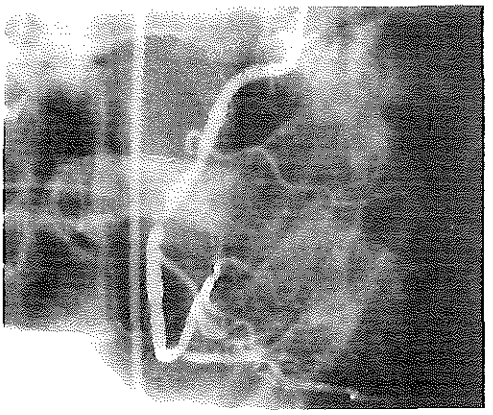

Figure 2A. *Right coronary artery restenosis.*

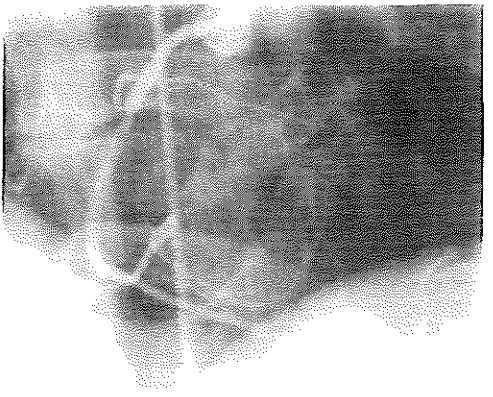

Figure 2B. *Distal perfusion during balloon inflation at 6 atmospheres.*

ing catheter and the balloon, more stiffness of the distal part of the shaft is required, to propel forward impulse towards the distal end of the balloon catheter. By eliminating the 20 cm long peel-away slit and by increasing shaft stiffness by extra brading, this problem may be overcome. With the current device, control angiography is better performed with the perfusion balloon retrieved to just proximal to the dilated segment, to allow recrossing and repeat dilatations if necessary. In all but 2 cases the catheter could be advanced toward the obstructing lesion. In one patient, mismatch of the diameter of the coronary artery reference diameter, minimal luminal diameter and catheter profile (1.3 mm, 0.4 mm and 1.24 mm respectively) was responsible for failure. In the other patient, a 2.5 mm perfusion balloon

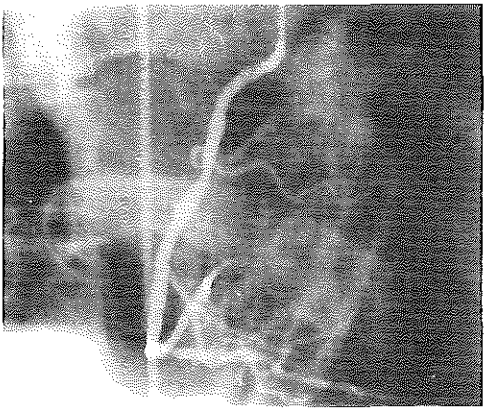

Figure 2C. *Final result.*

(profile 1.24 mm) got obstructed in the center of a narrow lesion (0.8 mm) of excessive length (20 mm), despite good backup support of the guiding catheter. In both instances conventional, large profile perfusion balloon catheters, probably also would have failed. Distal perfusion was demonstrated to be present by contrast injection. Inflations were well tolerated and associated with no or minor EKG changes, absent or tolerable anginal complaints during prolonged inflations and absence of hemodynamic deterioration.

These results demonstrate that this promising perfusion catheter further reduces the limitations of 6F guiding catheters. However, the performance of this device can still be improved through advances in technology.

SUMMARY AND CONCLUSIONS

A new low profile perfusion balloon catheter was used as a primary device in combination with 6F guiding catheters in 12 patients. It was demonstrated that these small sized guiding catheters do accommodate the ACS Flowtrack 40 well and that distal coronary artery perfusion was present in all patients during balloon inflation. Although performance of this device can still be improved, use of 6F guiding catheter no longer precludes the use of a perfusion balloon catheter.

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CHAPTER 4.4.2

POTENTIAL SOLUTIONS

RADIAL ARTERY AS ENTRY SITE

Feasibility of bailout techniques with 6 French guiding catheters

BAILOUT TECHNIQUES FOR FAILED CORONARY ANGIOPLASTY USING 6 FRENCH GUIDING CATHETERS

F. Kiemeneij, G.J. Laarman

Cathet Cardiovasc Diagn 1994;32:359-366

Catheterization and Cardiovascular Diagnosis 32:359–366 (1994)

Preliminary Reports . . . works in progress

Bailout Techniques for Failed Coronary Angioplasty Using 6 French Guiding Catheters

Ferdinand Kiemeneij, MD, and Gert Jan Laarman, MD, PhD

Coronary angioplasty (PTCA) through 6 French (F) guiding catheters is feasible, although acute or threatened closure following coronary artery dissections may occur. This report describes our experience with the treatment of suboptimal results in 13 patients from a population of 144 patients who had PTCA through 6F guiding catheters. Patients were treated with a new low profile autoperfusion catheter (ACS®, Flowtrack40™) or with Palmaz Schatz stents, advanced through 6F guiding catheters. PTCA was performed via the radial artery in 11 pts (85%) or via the femoral artery in two patients (15%). In two patients, (15%) PTCA was complicated by an dissection associated with complete loss of flow (TIMI 0) and a dissection was considered to lead to abrupt closure in the remaining 11 patients (85%), despite the presence of normal flow. A Flow-track40™ perfusion catheter was successfully applied in three of four patients. In one patient a persisting dissection after restoration of flow by a perfusion catheter was treated with three Palmaz Schatz stents. Implantation of Palmaz Schatz stents was attempted as primary technique in nine patients. In one patient the stent could not cross a dissection in the proximal LAD via the radial artery. With an 8F system via the femoral artery, two stents could successfully be deployed with the stent delivery system. In another patient the stent could not be advanced across a subtotal residual stenosis in a tortuous left anterior descending coronary artery. Despite normal antegrade flow and emergency bypass surgery, this patient developed a non-Q-myocardial infarction. In the remaining patients, the clinical course was uncomplicated. With the limitations of the bare stent technique kept in mind, applying bailout techniques such as perfusion balloons and implantation of bare Palmaz Schatz coronary stents should be considered for improvement of suboptimal angioplasty results in a selected group of patients after PTCA with 6F guiding catheters. © 1994 Wiley-Liss, Inc.

Key words: PTCA, dissection, bailout, stenting, perfusion balloons

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INTRODUCTION

Since the introduction of percutaneous transluminal coronary angioplasty (PTCA), a trend toward downsizing of balloon catheters was associated with considerable miniaturization of guiding catheters. PTCA through 6 French guiding catheters can safely be performed [1–3]. However, despite improvement of material, PTCA still carries a risk for dissection and acute coronary artery occlusion [4,5].

The use of 6F guiding catheters was supposed to exclude techniques such as perfusion balloon catheters and coronary stent implantation to improve suboptimal PTCA results. This report describes our experience in the management of suboptimal PTCA results and impending acute occlusion after PTCA through 6F guiding catheters.

MATERIALS AND METHODS

Definitions

A PTCA was considered to be suboptimal if the residual diameter stenosis exceeded 40% or if dissections were visible with established or impending loss of flow. From the geometry of the coronary segment, reference diameter, minimal luminal diameter, and diameter stenosis were derived (Quantitative Coronary Analysis by Philips DCI, Philips Medical Systems, Best, The Netherlands).

Dissections were classified according to the definitions described by Dorros et al. [4]. The perfusion status of the target vessel was classified according to the grading system of the Thrombolysis In Myocardial Infarction (TIMI) study [6]. Lesion morphology was classified according to the definitions established by an American College of Cardiology/American Heart Association task force [7].

Study Population

The study population was retrieved from 144 patients who underwent balloon angioplasty through 6F guiding catheters in our department between August 1992 and August 1993. This group comprised 13 subjects (9%), aged 64 ± 12 years, with a suboptimal PTCA result. A majority of patients (92%) were in CCS class III or IV, and one patient (8%) had nonexertional angina. Three patients had prior PTCA (23%) and one patient had prior coronary bypass surgery (8%).

Medical Treatment After Stent Implantation

All patients received Heparin 5,000 IU after insertion of the arterial introducer sheath. This dose was repeated if the procedure lasted > 1 hr. Nifedipin 10 mg was administered sublingually. Before angiography and following PTCA, nitroglycerin 100–300 mgr intracoronary was administered and repeated if indicated.

At the moment the decision of stent implantation was made, an additional bolus of Heparin 5,000 IU was given and Dextran 40 was administered, the first 500 ml at a rate of 100 ml/hr, the second 500 ml at a rate of 50 ml/hr. After stent implantation, dipirydamole 225 mg/d and acetosalicylic acid 300 mg/d was started. The introducer sheath was removed immediately after the transradial procedure. After transfemoral stent implantation, the sheath was withdrawn at an Activated Partial Thromboplastin Time (APTT) under 60 sec.

At 3 hr after hemostasis was achieved, 3,000 IU heparin was administered intravenously. Heparin was titrated to APTTs of 80–100 sec until stable adjustment on oral anticoagulant drug therapy (3 consecutive therapeutic Thrombotests) was obtained. Coumadin was given for 3 mo and acetosalicylic acid and dipyridamole were given for 6 mo.

Materials

PTCA Catheters. For this study, Scimed® 6F Triguide-Elite™ guiding catheters were used. These catheters are 100 cm long and have an inner diameter of 0.060" (1.53 mm). We used compliant rapid exchange balloon catheters (Scimed® Express™), the size being determined by the reference diameter of the target segment and the inflation pressure applied.

Perfusion balloon catheters. The perfusion balloon catheter used was the ACS® RX Flowtrack™40. Flow rate is 40 cc/min. This rapid exchange (20 cm "peelaway") catheter consists of a 135-cm-long Dynacross™ shaft (proximal 2.3F and distal 3.5F). The shaft has 14 perfusion holes, 0.014" in diameter, 10 proximal and 4 distal from the balloon. The balloon is made of PE-600. Rated burst pressure is eight atmospheres.

The balloon was inflated up to eight atmospheres. Presence of distal flow, defined as distal contrast opacification of the coronary artery during balloon inflation and the contrast agent disappearing after a few cardiac cycles, was angiographically assessed. The guiding catheter and guidewire were subsequently withdrawn proximal to the shaft marker in order to maximize perfusion. Balloon inflations of at least 300 sec were attempted.

Stents. A 15-mm Palmaz Schatz coronary stent (Johnson & Johnson Interventional Systems, Warren, NJ) was manually crimped on the balloon catheter, so that the balloon marker was positioned in the middle of the stent and no free movement from the stent over the balloon was noted. The primary used balloon catheter was used as stent carrier, because its increased profile after the first inflations will allow better fixation for the stent, compared to a balloon, tightly wrapped on the catheter shaft. The balloon was cleaned with saline to remove contrast agent, possible blood clots, and lubricating coating. The stent loaded balloon catheter was advanced over the guidewire toward the stenosis, under concomitant contrast medium delivery. After delivery, the stent diameter was optimized by successive dilatations with higher inflation pressures or with larger balloon catheters.

Strategies for Improvement of PTCA-Results

Conventional means to obtain improvement of suboptimal results comprised administration of nitrates, calcium antagonists, additional heparin, or prolonged inflation with the dilatation catheter. Stenting as first choice bailout technique was performed if the perfusion balloon was too short to cover the dissection, if the dissection persisted or extended under prolonged dilatations with the dilatation catheter, or in the initial phase of this study when no low profile perfusion balloons were available. Treatment with a perfusion balloon was attempted first if the vessel was not suitable for stenting or if contraindications for anticoagulation precluded stent implantation. Stent implantation following the use of a perfusion balloon was performed if the result of prolonged dilatations was considered suboptimal.

RESULTS

In 11 patients (85%), PTCA was performed via the radial artery after confirmation of collateral, ulnar blood supply to the hand, by performing the Allen test.

PTCA was performed via the femoral artery in two patients (15%). Baseline quantitative coronary data and details on lesion severity and morphology before and after PTCA and after repair are shown in Table I. Complex lesion morphology (Types B and C) was seen in 10 patients (77%). In all patients, major dissections formed the reason to to apply a bailout technique; 11 patients had normal coronary perfusion but a residual stenosis $\geq$ 45% (85%) and 2 patients had an occlusive dissection (15%).

Ballout Techniques

The Flowtrack 40 perfusion catheter was used as primary device in four patients. The catheter could be positioned and retrieved without problems.

Mean duration of balloon inflations (1–3 inflations per patient) was 450 sec (range 300–900 sec). During balloon inflation, coronary flow distal to the balloon could angiographically be demonstrated in all patients. Al-

TABLE I. Lesion Characteristics Before and After PTCA and After Intervention*

		Pre-PTCA			Post-PTCA				Final result		
No.	CA	%DS/TIMI/Lesion[a]			%DS/TIMI/Diss[b]			Strategy	%DS/TIMI/Diss		
1	LAD	76	3	A	100	0	E	PSS (1)	22	3	—
2	LAD	72	3	C	55	3	B	PSS (1)	22	3	B
3	LAD	60	3	A	45	3	A	PSS (1)	20	3	—
4	LAD	60	3	C	66	3	B	FT 900 sec	35	3	B
5	LCX	73	3	B	51	3	A	PSS (1)	19	3	A
6	LAD	70	3	B	68	3	A	PSS/UCABG	68	3	A
7	LAD	64	3	B	50	3	C	PSS (2)	21	3	—
8	LAD	75	3	B	45	3	B	PSS (1)	5	3	—
9	LAD	57	3	C	50	3	B	PSS (2)	21	3	B
10	LCX	66	3	B	60	3	B	PSS (2)	27	3	—
11	RCA	72	3	C	100	0	C	FT/PSS (3)	29	3	B
12	LAD	79	3	A	50	3	A	FT 300 sec	7	3	—
13	LAD	50	3	B	45	3	B	FT 300 sec	21	3	—
Mean±1SD		67 ± 9%			60 ± 19%				24 ± 15%		
Median		70%			51%				21%		

*Abbreviations: CA = coronary artery; %DS = percent diameter stenosis; TIMI = Thrombolysis In Myocardial Infarction flow grading; LAD = left anterior descending coronary artery; PSS = Palmaz Schatz stent: (n) number implanted; FT = Flowtrack perfusion catheter; UCABG = urgent coronary artery bypass grafting; LCX = left circumflex coronary artery; RCA = right coronary artery.

[a]See ref. [7] for lesion morphology classification.

[b]See ref. [4] for dissection classification.

though these patients had chest pain of moderate severity, no major EKG-changes and no hemodynamic deterioration were recorded.

Angiographical results were satisfactory in three patients (Table I). Clinical course was uneventful, and these patients were discharged the next day.

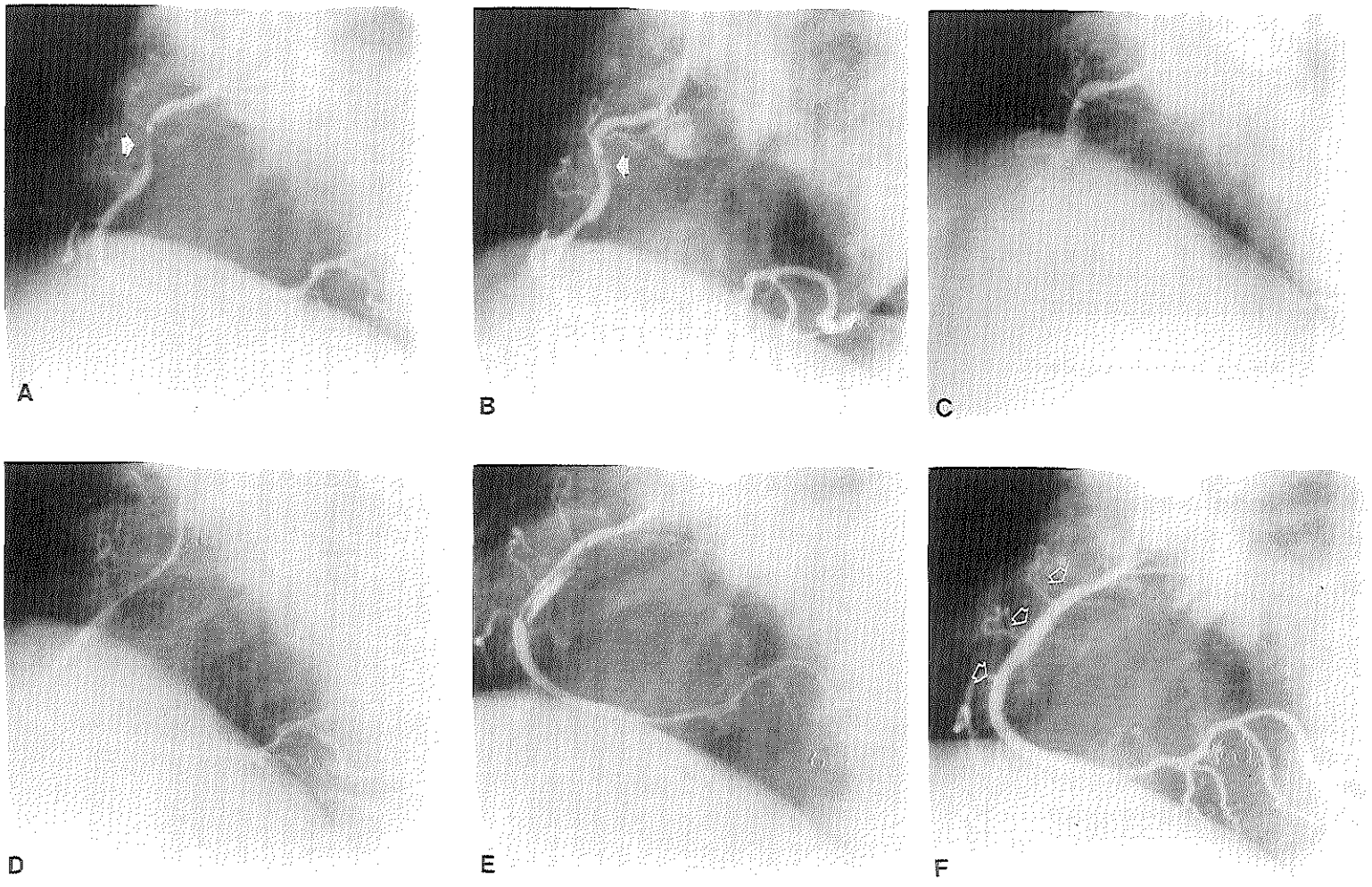
In one patient with a total occlusion of the right coronary artery, 1 hr after PTCA, flow could be restored with a Flowtrack catheter (Fig. 1). After balloon deflation, a large dissection persisted. Three 15-mm stents were successfully implanted to cover the dissection. Cardiac enzymes remained normal and no electrocardiographical signs of myocardial infarction were present.

In nine patients implantation of a Palmaz Schatz stent was attempted as primary technique; in four patients, no Flowtrack was available, and in four patients the dissection was considered too long or too complex. In one patient, a stent was selected because no major change in morphology of a short dissection in the LAD was observed despite two high pressure dilatations of 1 min duration with an adequate-size balloon (Fig. 2). In this patient, the stent-loaded balloon catheter could not be advanced across the lesion. During attempts to reach the stenosis, the stent partially slipped from the balloon. Instead of retrieving the stent from the LAD, with the risk of stent loss and embolization, the operator was forced to deploy the stent proximal from the lesion. Since attempts to recross the stenosis with other balloons also failed, the patient was referred for bypass surgery in a stable condition. Postoperative course was complicated by a non-Q-myocardial infarction (CKMB 79 IU/l).

Transradial artery stent implantation failed in another patient with a significant residual stenosis and type B dissection after PTCA for a proximal LAD restenosis (Fig. 3). Six guiding catheters were used before enough support was obtained to allow passage of the balloon catheter across the stenosis. Three attempts to cross the dissection with a stent-loaded balloon failed, due to insufficient guiding catheter support and poor coaxial alignment of the guiding catheter. Through an 8F FL4 guiding catheter via the right femoral artery, two stents were successfully implanted, with use of the sheath protected Stent Delivery System (Johnson & Johnson). In this patient, the clinical course was complicated by groin bleeding, necessitating a blood transfusion. Transradial artery stent implantation was successful in the remaining seven patients and clinical course was free of death, myocardial infarction, bypass surgery, rePTCA, and bleeding complications.

DISCUSSION

Since the introduction of PTCA for treatment of coronary artery disease, angioplasty equipment has been miniaturized. Low profile balloon catheters can now be used in association with 6F guiding catheters [1–3] and in selected cases even with 4F diagnostic catheters [8]. The major advantage is the smaller arterial puncture hole, a key factor in preventing postprocedural vascular complications. Another advantage is the possibility to select smaller arteries as entry site, such as the brachial artery [9] and radial artery [3].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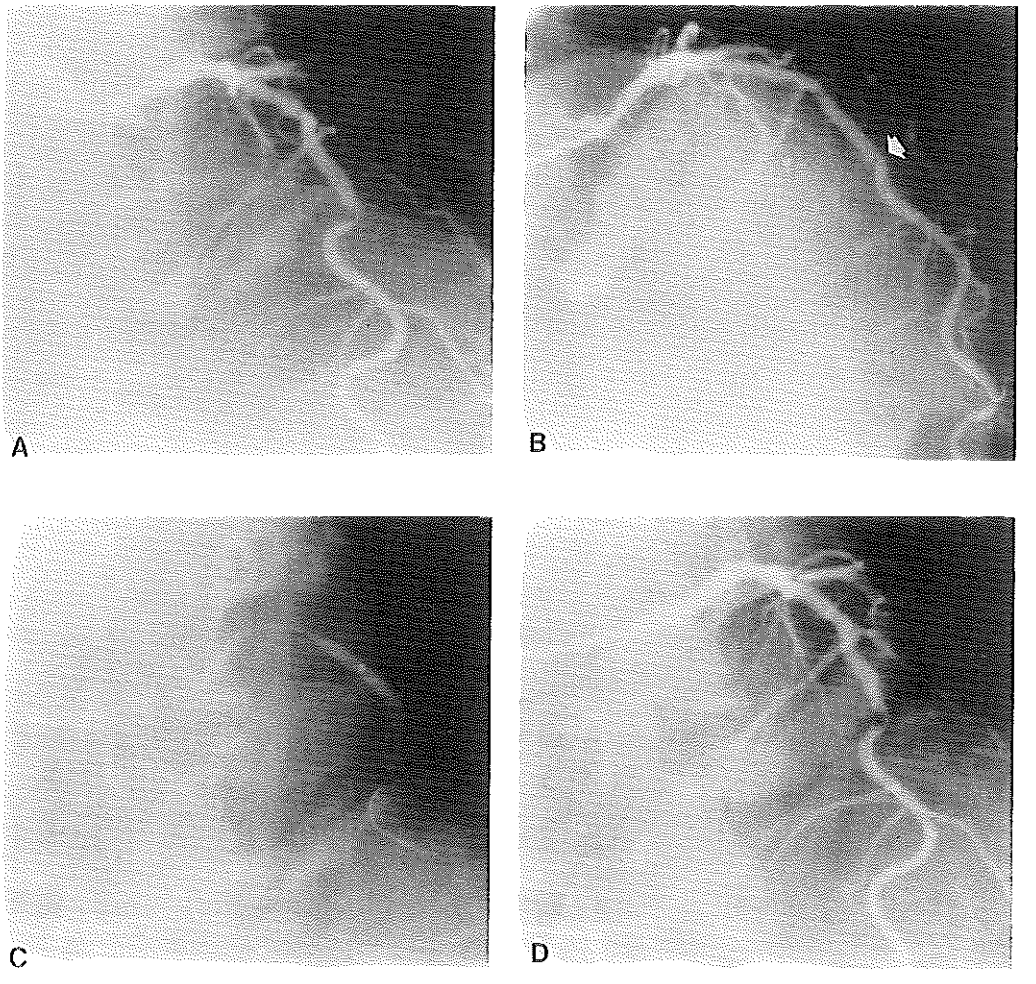

Fig. 2. A. Type B lesion in a tortuous left anterior descending coronary artery. B. After balloon dilatation, a significant residual stenosis and type A dissection (arrow). C. Deployment of a 15-mm Palmaz Schatz stent proximal from the stenosis. D. Final result after attempts to recross the stenosis formed indication for bypass surgery.

Fig. 1. A. Type B lesion in the right coronary artery (arrow). B. After PTCA, a dissection type B was visible (arrow). C. RCA was totally occluded 1 hr later. D. Flow was restored with a Flowtrack 40 3.0 perfusion catheter. E. After balloon deflation, a residual stenosis and dissection type C were appreciated. F. Result following implantation 3 Palmaz Schatz stents was optimal (arrows).

The radial approach is especially attractive because the superficial course of this artery, together with the absence of major nerves and veins near the distal radial artery, allows effective hemostasis and is associated with low risk for puncture site-related complications, such as bleeding, arteriovenous fistula, and nerve damage, and with early patient ambulation. In 100 patients in whom a transradial PTCA was attempted, no major puncture site-related bleeding complications were encountered [3].

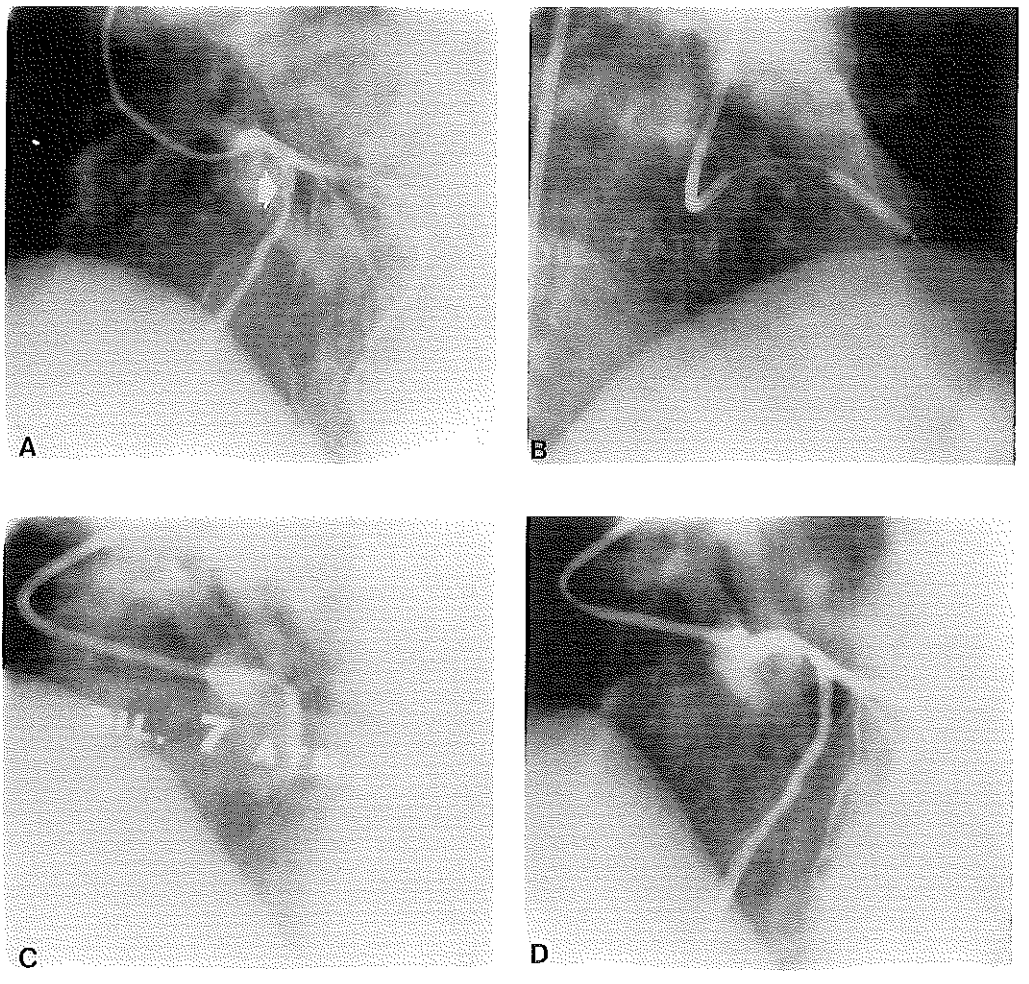

Fig. 3. A. Dissection in the proximal LAD (arrow). B. Deployment of the distal stent with the stent delivery system. C. Deployment of the proximal stent with the stent delivery system. D. Final result.

Early asymptomatic radial artery occlusion was present in 10 patients (10%), but in five patients (50%) spontaneous recanalization of this artery was encountered. Procedural success was 98% (92/94 pts via the radial artery and 6/6 pts via the femoral or brachial artery). However, the inner diameter of 6F guiding catheters may compromise the use of large catheter systems, such as perfusion balloons, stent delivery systems, atherectomy catheters, and the current catheters for intravascular ultrasound. Prolonged dilatations with perfusion balloons may be required to improve acute suboptimal PTCA results [10] or to stabilize the patient before emergency coronary bypass surgery after failed PTCA [11], if stent implantation is impossible or contraindicated.

We recently reported on the successful use of the Flowtrack 40 perfusion catheter as a primary device through 6F guiding catheters [12]. The present study illustrates that the use of a low profile ACS®

FLowTrack®40 perfusion balloon catheter can be attempted to restore coronary geometry in the treatment of dissections after PTCA, with adequate distal perfusion during balloon inflation. Thus, 6 French guiding catheters no longer preclude the use of this bailout technique.

Implantation of Palmaz Schatz stents is an effective technique to stabilize patients after suboptimal PTCA results despite a reported higher incidence of subacute stent thrombosis, compared to elective stenting [13–17]. At suitable coronary anatomy, stenting may be the strategy of choice if results of prolonged inflations are suboptimal, if these inflations are poorly tolerated by the patient or if the dissection is to long to be covered by the perfusion balloon. Stent implantation through 6F guiding catheters has been reported by Urban et al. [18] and by our group [19], which has the potential for a reduction of bleeding complications, compared to stent implantation via 8F guiding catheters. We recently described 20 patients who underwent successful stentimplantation via the radial artery with 6F guiding catheters (ms. accepted). No subacute stent thrombosis and major local bleeding complications were encountered in this small series.

During continued experience by our group (50 patients), 63 stents were successfully implanted (procedural success; 96%) and no stent thrombosis or major entrysite bleeding complications were noted (unpublished data). The procedural success of the transradial technique is comparable with procedural results in the multicenter Benestent study where all patients received a stent via the femoral artery. Bare stents as well as sheath-protected systems were used in this study. Of 251 patients in whom stent implantation was attempted, procedural success was 92.3%. Inability to cross the lesion with a stent occurred in 16 patients, and in 1 patient a significant stenosis persisted [20]. The femoral, sheath-protected stent technique as applied in the multicenter STRESS trial had a procedural success of 96.1% [21].

However, two limitations of the transradial, bare stent technique are illustrated in the current report. Preshaped catheters (e.g., Amplatz, Judkins curves) are designed for the femoral approach, whereas the approach from the right arm often compromises the properties of these catheters, such as adequate support for passage of unprotected stent-loaded balloons over the target coronary lesion. This problem was encountered in one patient where 6F Judkins Left and other catheters did not provide enough support and coaxial alignment. Via the femoral artery, enough support of an 8F Judkins Left-curved catheter obtained to allow passage of a stent delivery system. In the other patient where the stent failed to cross a mid-LAD dissection, an attempt with the SDS also would have failed since balloon catheters of lower profile could not be advanced over the dissected segment.

A limitation of both the bare stent technique as the sheath-protected technique is the inability to cross tortuous coronary segments and tight lesions. Since only the bare stent technique can currently be applied in combination with 6F guiding catheters, stent displacement and embolization remain serious hazards during attempts to advance the system over curves and severe obstructions and during retrieval of the stent-loaded balloon in the guiding catheter, as was the case in one patient. In such a situation, both the stent-loaded balloon catheter and the guiding catheter need to be withdrawn, preferrably over the intracoronary guidewire. This maneuver carries considerable risk for losing distal access by inadvertent loss of guidewire position. To circumvent this problem, the stent can be deployed proximal from the target lesion, provided that coronary anatomy is suitable for stenting.

With these limitations in mind, applying bailout techniques such as perfusion balloons and implantation of bare Palmaz Schatz coronary stents should be considered for improvement of suboptimal angioplasty results in a selected group of patients after PTCA with 6F guiding catheters.

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CHAPTER 4.5.1

POTENTIAL SOLUTIONS

RADIAL ARTERY AS ENTRY SITE

Transradial coronary angioplasty

TRANSRADIAL ARTERY CORONARY ANGIOPLASTY

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CLINICAL INVESTIGATIONS

Transradial artery coronary angioplasty

This study explored the feasibility and safety of percutaneous coronary balloon angioplasty (PTCA) with miniaturized PTCA equipment via the radial artery. Coronary angioplasty (PTCA) via the femoral or brachial arteries may be associated with rare vascular complications such as bleeding and damage to the artery and adjacent structures. It was postulated that PTCA via the radial artery with miniaturized angioplasty equipment is feasible and that no major puncture site-related complications occur because hemostasis is obtained easily and because no major structures are near the radial artery. With double blood supply to the hand, radial artery occlusion is well tolerated. In 100 patients with collateral blood supply to the right hand, PTCA was attempted with 6F guiding catheters and rapid-exchange balloon catheters for exertional angina (87 patients) or nonexertional angina (13 patients). Angioplasty was attempted in 122 lesions (type A $n = 67$ [55%], Type B $n = 37$ [30%], and type C $n = 18$ [15%]). Pre- and post-PTCA computerized quantitative coronary analysis was performed. Radial artery function and structure were assessed clinically and with Doppler and two-dimensional ultrasound on the day of discharge. Coronary catheterization via the radial artery was successful in 94 patients (94%). The 6 remaining patients had successful PTCA via the femoral artery ($n = 5$) or the brachial artery ($n = 1$). Procedural success (120 of 122 lesions) was achieved in 92 patients (98%) via the radial artery and in 98 patients of the total study population. Minimal luminal diameter increased from 0.9 ± 0.3 (0 to 1.8) to 2.0 ± 0.5 (0.6 ± 3.6) mm, and diameter stenosis was reduced from 74% ± 11% to 24% ± 11%. In 3 patients a coronary stent was implanted via the radial artery because PTCA results were suboptimal. Of 98 patients with a successful PTCA, four (4%) had acute myocardial ischemia 1 to 24 hours after the procedure. In these patients an emergency second PTCA procedure via the femoral artery was performed successfully, but in 2 patients a myocardial infarction could not be prevented. No other major cardiac complications were encountered. No major entry site-related complications were seen, and no patient required vascular surgery or blood transfusions. In 10 patients radial artery pulsations were absent at discharge, and all 10 were asymptomatic. Of these 10 patients, late recanalization was evident in 5, and in 3 patients pulsations remained absent. PTCA via the radial artery is effective and safe and minimizes major puncture site-related complications. (Am Heart J 1995;129:1-7.)

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The external diameter of the guiding catheter used during the first percutaneous transluminal coronary angioplasty (PTCA) was 9.4F.[1] At present PTCA is most commonly performed with 8F F guiding catheters. The use of these large-bore guiding catheters in conjunction with aggressive anticoagulation may contribute to uncommon but severe entry site–related complications such as bleeding, pseudoaneurysms, arteriovenous fistula, nerve damage, and arterial occlusion.

Low-profile rapid-exchange balloon catheters permit use of miniaturized guiding catheters while maintaining the advantages of over-the-wire systems: free guide wire movement and the ability to exchange balloons of different diameters with maintenance of distal access. The performance of 6F guiding catheters with regard to contrast delivery, pressure monitoring, and backup support is ade-

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Table I. Baseline characteristics

	n (%)
Patients	100
Gender	
Male	77
Female	23
Age (yr)	62 ± 10 (34-82)
Height (cm)	172 ± 8 (154-190)
Weight (kg)	78 ± 10 (54-100)
Oral anticoagulation*	
Acetylsalicylic acid	80
Dipyridamol	4
Coumadin	10
Angina (CCS class)	
Exertional	87
I	1
II	5
III	67
IV	14
Nonexertional	13
Previous myocardial infarction	45
Previous bypass surgery	14
Hypertension	37
Diabetes mellitus	11
Cholesterol ≥6.5 mmol/L	33
Cigarette smoking	58
Family history	43

CCS, Canadian Cardiovascular Society.
*Not mutually exclusive.

quate,[2] and pressure damping by the guiding catheter is encountered less frequently than with 8F guiding catheters. With these smaller guiding catheters, arterial puncture holes also become smaller, making possible fewer bleeding complications, shortened hemostasis time, and early ambulation. Another potential advantage of 6F guiding catheters is the possibility to select smaller arteries, such as the brachial or radial artery, as the entry site for PTCA. The safety of transradial coronary angioplasty is determined mainly by the favorable anatomic relations of the radial artery to its surrounding structures. No major veins or nerves are located near the radial artery, minimizing the chance of related injury to these structures. Because of the superficial course of the artery, hemostasis can be obtained easily by local compression. Thrombotic or traumatic artery occlusion does not endanger the viability of the hand, if adequate collateral blood supply by the ulnar artery is present. The purpose of this study was to explore the feasibility and safety of transradial artery PTCA with 6F guiding catheters and low-profile rapid-exchange balloon catheters in 100 patients.

METHODS

Patient selection. From six interventional practitioners in our group, first one and in a later phase two investigators performed this feasibility study. Suitability to participate in this study with regard to local vascular and cardiac status was assessed at the arrival of the patient in the catheterization laboratory. The radial and ulnar artery pulsations were examined and the Allen test performed. The result of the Allen test was considered normal when after compression of both ulnar and radial arteries the normal color of the hand returned within 10 seconds after release of the ulnar artery. Because neither investigator was experienced with the transradial approach, a greater number of ideal candidates were selected in the early phase of this study. In a later phase, however, unstable angina, multivessel PTCA, complex lesion structure, and venous bypass graft stenosis formed no reason to exclude patients from this approach. Exclusion criteria were evident heart failure requiring right heart catheterization, expected hemodynamic deterioration during balloon inflation, the need for intraaortic balloon pumping (for example, during PTCA of the "last remaining vessel"), and PTCA for chronic total occlusions.

Medical preparation. Before the procedure diazepam, 5 mg was administered orally. Immediately after insertion of the arterial introducer sheath, heparin, 5000 IU was administered. The same dose was given for each hour during the procedure. Activated partial thromboplastin time (APTT) was not monitored during the procedure. One to 2 hours after immediate sheath removal and local hemostasis, heparin infusion was begun and continued overnight, titrated to APTT values of 60 to 80 seconds (normal 30 to 40 seconds) in case of evidence of intracoronary thrombosis or dissection. Before initial and final angiography (Hexabrix 320) intracoronary nitroglycerin, 100-300 μg was administered and repeated on indication during the procedure. Nifedipin, 10 mg was given sublingually in case of radial or brachial artery spasm.

Catheterization and angioplasty

Radial artery catheterization. The right arm, supported by a sideward extension of the catheterization table, was abducted to 70 degrees, and the wrist was hyperextended. After local anesthesia with lidocaine 2%, the anterior wall of the radial artery was punctured with an arterial introducer needle or with a 22-gauge radial artery catheterization needle (Arrow International, Reading, Pa.) set at 45 degrees 1 cm proximal from the styloid process. After appearance of pulsatile flow from the Arrow needle, a 0.025-inch, 260 cm straight guide wire (Angiomed, Karlsruhe, Germany) was introduced; this set does not allow passage of a larger wire. An Angiomed 0.035-inch, J-tipped guide wire was advanced if an arterial introducer needle was used. A small skin incision was made with a number 11 surgical blade, followed by insertion of a 6F 10 cm arterial introducer (Hemaquet II, Bard, Billerica, Mass.).

Coronary artery cannulation. The position of the operator at the catheterization table was similar to that during the femoral approach. A guiding catheter (Scimed Life Systems, Maple Grove, Minn.; inner diameter 0.060 inch, shaft length 100 cm) was selected with an appropriate curve to provide maximal backup support during angioplasty. The guiding catheter was advanced over a long (260 cm)

0.025-inch guide wire positioned in the aortic root. The right coronary artery was cannulated with Judkins Right catheters and with multipurpose or El Gamal catheters. Cannulation of the left coronary artery with a Judkins Left catheter requires special manipulation: over the guide wire, the catheter tip must be advanced and turned toward the coronary ostium. When the primary curve of the catheter reaches the aortic valve, withdrawal of the guide wire results in angulation of the secondary curve, which causes the tip of the catheter to be lifted toward the coronary ostium. We used the Judkins Left catheter as a first choice, followed by multipurpose and Amplatz catheters.

Angiography. Computerized quantitative coronary analysis was performed with the DCI Polydiagnost C2 x-ray imaging system (Philips Medical Systems, Best, The Netherlands). Pre- and post-PTCA single-plane digital coronary angiography was performed under standard conditions to permit quantitative analysis. We used automated edge-detection software to analyze digital radiographic images, with the guiding catheter as the calibration standard. From the shape of the coronary segment, the reference diameter, minimal luminal diameter, and diameter stenosis were derived. The perfusion status of the target vessel was classified according to the grading system of the Thrombolysis in Myocardial Infarction (TIMI) trial.[3] The morphologic types of the lesions were determined according to the definitions established by an American College of Cardiology–American Heart Association Task Force.[4] Coronary artery dissections were defined according to the classifications described by Dorros et al.[5]

Angioplasty. After angiography a 0.014-inch guide wire (High Torque Floppy, Advanced Cardiovascular Systems, Santa Clara, Calif.) was advanced across the lesion. Over this guide wire a rapid-exchange, low-profile, compliant balloon catheter (Scimed Express) was positioned at the stenosis. Inflation pressures were adjusted according to balloon diameters given by the manufacturer and the reference diameters of the target segments. Performance of the guiding catheter (back-up support, opacification of the target vessel, and pressure monitoring) and of the balloon catheter (crossability and retrievability) were semiquantitatively scored as good, moderate (no need to change guiding or balloon catheter), or poor (need to change guiding or balloon catheter).

Introducer sheath removal and hemostasis. The arterial sheath was removed directly after withdrawal of the guiding catheter, followed by application of a tourniquet at the radial puncture site. The tourniquet was released gradually over a 15- to 30-minute period. After hemostasis had been achieved, a pressure bandage was applied over the punctured artery for 6 hours. Patients were not restricted to bed rest but were advised to refrain from movements of the wrist joint.

Predischarge examinations. The radial artery was evaluated for the presence of pulsations. The Allen test was repeated. The reversed Allen test, the result of which is normal when after compression of ulnar and radial arteries the hand becomes normally colored <10 seconds after release of the radial artery, also was performed. Claudication of the hand was tested by asking the patient to open and close the hand 50 times. A two-dimensional and Doppler ultrasound study was performed just before discharge. If radial artery pulsations or flow were absent, an ultrasound study was repeated after 1 to 3 months.

Table II. Angiographic data

	n	%
Distribution of lesions (*n* = 122)		
LAD	51	41
RCA	24	20
LCX	22	18
OM	16	13
Diagonal	6	5
VBG	2	2
RDP	1	1
TIMI grade		
0	3	2
1	1	1
2	5	4
3	113	93
Type of lesion (*n* = 122)		
A	67	55
B	37	30
C	18	15
Calicified lesion	8	7
Thrombus at lesion	2	2
Dissection	1	1

LAD, Left anterior descending coronary artery; *LCX*, left circumflex coronary artery; *OM*, obtuse marginal branch; *RCA*, right coronary artery; *RDP*, right descending posterior branch; *TIMI*, Thrombolysis in Myocardial Infarction trial; *VBG*, venous bypass graft.

Definitions of success. *Procedural success* was defined as <50% residual stenosis and normal flow without procedural major cardiac complications such as death, acute myocardial infarction, or coronary bypass surgery. *Clinical success* was defined as procedural success, absence of cardiac complications, and no need for second PTCA from the moment the guiding catheter was withdrawn from the patient.

RESULTS

Study population. Between August 1992 and April 1993, 660 patients underwent PTCA in our department. From the 430 patients assigned to the two investigators, 100 patients were selected for transradial artery balloon angioplasty. Clinical baseline characteristics are summarized in Table I.

Angiographic data Distribution of angioplasty lesions, TIMI grade flow, and morphologic types of lesions are presented in Table II. Reference diameter of target segments was 2.5 ± 0.5 (1.4 to 4.2) mm, minimal luminal diameter 0.9 ± 0.3 (0 to 1.8) mm, and diameter stenosis 74% ± 11% (30% to 100%).

Procedure

Radial artery cannulation. The radial artery was

Table III. Balloon catheter selection and inflation characteristics

	n	%
Total	104	
Balloon diameter (mm)		
2.0	14	13
2.5	53	51
3.0	34	33
3.5	3	3
No. of inflations	2.9 ± 1.1 (1-7)	
Pressure (atm)	10.6 ± 1.9 (6-15)	
Balloon size during inflation (mm)	3.0 ± 0.5 (1.9-4.1)	

successfully punctured and cannulated in 96 patients (85% within 5 minutes). In 3 patients radial artery puncture failed, and in 1 patient the guide wire could not be advanced, leading to temporary staining of contrast medium in the radial artery vessel wall. Three of these patients had successful PTCA via the femoral artery and 1 via the brachial artery. No procedural complications leading to functional disability of the hand or requiring vascular surgery were encountered.

Guiding catheter selection and performance. Coronary artery cannulation with 6F guiding catheters was successful in 94 (98%) of 96 transradial artery procedures (89% within 5 minutes). In 1 patient the procedure had to be discontinued because of severe spasm of the radial artery. In another patient the guiding catheter could not be advanced beyond a tortuous subclavian artery. Both patients had successful PTCA via the femoral artery. One hundred forty-seven guiding catheters (1.47 catheters per procedure) were selected before the coronary artery was cannulated. For the left coronary artery 1.51 ± 1.09 and for the right coronary artery 1.2 ± 0.65 guiding catheters were used (p not significant). Inability to engage the ostium of the coronary artery and kinking of the shaft after excessive manipulations of the guiding catheter were the major reasons for failure. For PTCA 103 catheters were finally used. The left coronary artery was cannulated with the Judkins Left (49%), multipurpose (35%), Amplatz (11%), and El Gamal (5%) catheters and the right coronary artery with Judkins Right (40%), multipurpose (30%), and El Gamal (30%) catheters. For these catheters, contrast opacification and pressure monitoring were rated good in 97% and 99% of instances, respectively. Backup support was good in 80% and moderate in 20% of cases.

Balloon catheter selection and performance. For 100 patients, 104 balloon catheters (1.04 balloons per patient) were used. Details on balloon size and inflations are given in Table III. Only 3 (3%) balloon catheters with a diameter of 3.5 mm were used because the compliant 3.0 mm dilatation catheters reach a diameter >3.5 mm at inflation pressures >11 atm. Larger vessels were not encountered frequently in this study. Difficulty in vessel opacification and balloon retrieval did not play a role in selection of the smaller balloon catheters. Passage of the dilatation catheter through the guiding catheter and crossability at the stenosis was rated good in 89% and moderate in 9% of cases. All balloon catheters were successfully retrieved, but 3 balloons were pulled back with noticeable friction.

Angiographic results. Procedural success was obtained in 92 (98%) of 94 transradial artery PTCAs and in the 6 PTCAs performed via the femoral or brachial arteries. Two (1.6%) lesions (reference diameter 1.9 and 1.8 mm, minimal luminal diameter 0.6 and 0.9 mm) could not be crossed with the dilatation catheter. In both patients a second attempt via the femoral artery with 8F guiding catheters and lower-profile balloon catheters also failed. Of 122 lesions, 120 (98.4%) were successfully crossed and dilated. Minimal luminal diameter increased to 2.0 ± 0.5 (0.6 to 3.6), mm and diameter stenosis was reduced to 24% ± 11% (0% to 68%). In three (3%) patients the final result was considered suboptimal because of an obstructive dissection at the angioplasty site; in these cases a Palmaz-Schatz stent (Johnson & Johnson Interventional Systems, Warren, N. J.) manually crimped on the same type balloon catheter was implanted, also via the radial artery, with an optimal result. At 10 (8%) angioplasty sites a type A^5 dissection and at 20 (16%) sites a type B dissection was visible. At 3 sites (2%), a minor side branch was occluded without clinical or electrocardiographic signs of ischemia. No other procedural complications were encountered. The procedure lasted 15 to 120 (mean 35 ± 17) minutes.

Hemostasis. Hemostasis was obtained 29 ± 15 (15 to 120) minutes after sheath removal. In one patient, collagen (Vasoseal) was applied subcutaneously near the puncture opening to stop prolonged leakage of blood.

Clinical course. The 2 patients in whom the attempt to cross the stenosis had failed had an uncomplicated clinical course. Of 98 patients with a successful PTCA, 4 (4%) patients had acute myocardial ischemia. One patient had chest pain and electrocardiographic changes 1 hour after PTCA of the left circumflex coronary artery (LCX) (11% residual stenosis, no dissection). At acute angiography the dilated segment showed no abnormalities, but a significant lesion was now visible more distally in the ves-

sel. The patient had an uncomplicated course after successful PTCA of that lesion. One patient had unstable angina pectoris 1.5 hour after successful PTCA of the LCX (30% residual stenosis, type B dissection). During acute angiography, a significant stenosis caused by dissection and thrombus was visible; subsequent PTCA was successful. A small (creatine kinase MB isoenzyme [CK-MB] 35 IU/L) non–Q-wave myocardial infarction developed in this patient. Another patient had a total occlusion 12 hours after PTCA of the left anterior descending coronary artery (LAD) (24% residual stenosis, type B dissection). Despite successful emergent second PTCA, the patient had a Q-wave anteroseptal infarction with a maximal CK-MB of 119 IU/L. One patient had three episodes of unstable angina, the first episode 24 hours after successful PTCA of the LAD for postinfarction angina pectoris (47% residual stenosis, type B dissection). This patient had three successful recanalizations for reocclusions of the LAD. None of these repeat PTCAs was followed by increases in CK-MB or development of new Q waves. All second PTCAs were performed via the right femoral artery. No emergent coronary artery bypass surgery was needed. No bleeding complications from the puncture site were recorded. Vascular surgery or blood transfusions were not required. Patients were discharged 1.6 ± 2.0 (0 to 14) days after angioplasty.

Radial artery assessments. Two-dimensional and Doppler ultrasound examination of the radial artery was performed in 97 patients (97%). An intimal lesion was seen in 11 (11%) patients. Two patients had a pseudoaneurysm at the puncture site. At follow-up one pseudoaneurysm spontaneously disappeared, and the other remained stable. In 10 (10%) patients the radial artery pulsations were absent at discharge, and the result of the reversed Allen test was negative (abnormal). These patients also had absent ($n = 8$) or diminished ($n = 2$) Doppler flow patterns. None of these patients had claudication or functional disability of the hand. Late recanalization at follow-up was clinically evident in 5 patients. In 3 patients, radial artery pulsations remained absent. Two patients with early radial artery deficit were not available for late follow-up.

DISCUSSION

At present there is a trend toward the downsizing of PTCA guiding catheters, from the 9.4F catheter in early experience with PTCA to the commonly used 8F catheters and the newer 7F,[6] 6F,[7] 5F,[8] and even 4F[9] guiding catheters. This evolution toward miniature equipment makes a small artery, such as the radial artery, suitable as an access site for PTCA. Campeau[10] performed transradial diagnostic heart catheterization in 100 patients with 5F catheters. In this series the coronary arteries were successfully reached in 88 patients; in 10 patients puncture or cannulation failed; and in 2 patients the coronary catheterization failed. Early and late pulse deficit occurred in 22 and 6 patients, respectively. Significant complications were arterial dissection in 1 patient and radial artery occlusion in another, both without signs of ischemia in the hand.

Our study was performed with 6F introducer sheaths and with a new 6F guiding catheter (Scimed Triguide). For the total study population, procedural success was 98% (98 of 100) and clinical success 94% (94 of 100). In patients in whom transradial artery angioplasty was completed, procedural success was 98% (92 of 94) and clinical success 95% (89 of 94). These results compare favorably with the literature on the conventional femoral approach.[5] In this early experience, we used only 0.025- or 0.035-inch Angiomed® guide wires for guiding catheter advancement. Although the 0.035-inch guide wire allowed more support, friction between this wire and the radial artery is felt by the operator more commonly. Ideally a more slippery guide wire of appropriate stiffness should be used. Because guiding catheters are changed more frequently, the use of 260 cm exchange wires also facilitates the procedure. The performance of guiding catheters with regard to backup support, passage of dilatation catheters, and visualization of coronary anatomy was satisfactory.

A large number (147) of guiding catheters were used because several catheters had to be replaced because prolonged manipulation caused kinking of the thin shaft. Preshaped catheters (e.g., Amplatz and Judkins) are designed for the femoral approach, whereas the approach from the right arm may compromise the properties of these catheters. A reason for not using the left radial artery to cope with this problem is a change of the position of the operator toward the left side of the catheterization table. This change requires major rearrangement of the catheterization table and laboratory especially if the monitors cannot be moved toward the right side of the table. The number of balloon catheters per procedure (1.04) was low as a result of the inflation pressure–dependent diameter of this compliant balloon, so that the final result could be obtained by a single balloon catheter. The High Torque Floppy guide wire performed well with regard to support for the balloon catheters and with regard to ability to cross the lesion. However, recanalization of chronic total occlusions was not attempted in this study. Stiffer guide wires may be more appropriate for this indica-

tion. The use of 6F guiding catheters has been questioned for inappropriateness for use with bailout devices such as coronary stents and perfusion balloon catheters.

In the present study, no stent was primarily implanted in patients with a type B dissection because residual stenosis was <50% and flow was not impaired. However, in three of these patients a postprocedure coronary artery occlusion developed. Three other patients in whom PTCA results were suboptimal because of an occlusive dissection were successfully treated by transradial artery implantation of a Palmaz-Schatz stent. The stent was manually crimped on the balloon catheter used. Palmaz-Schatz stent implantation via 6F guiding catheters has been reported by Urban et al.[11] The transradial artery approach for stent implantation through 6F guiding catheters has recently been studied by our group[12] in a series of 20 patients. No attempt to optimize suboptimal results with long inflations by using a perfusion balloon was made because during this study no low-profile perfusion balloon catheters were available. In another recent report, however, we[13] described satisfactory results of angioplasty through 6F guiding catheters with a new perfusion balloon (ACS Flowtrack 40) as primary device in 14 patients.

An important finding in the present study is the absence of major vascular complications such as significant bleeding, need for vascular surgery, and functional disability of the hand. Radial artery occlusion after the procedure (10 patients) and at follow-up (3 patients) was higher than would be expected at the femoral or brachial artery sites but was surprisingly low when compared with the 30% and 38% incidences of radial artery occlusion reported by Davis and Stewart[14] and by Bedfort and Wallman,[15] respectively after prolonged cannulations of the radial artery for blood pressure monitoring. Early withdrawal of the sheath, immediately after angioplasty, may be an important factor in the prevention of radial artery thrombosis. However, an 2% incidence of pseudoaneurysm formation may be related to sheath removal during anticoagulation.

Symptoms of radial artery occlusion were absent in our study because only patients with collateral blood supply to the hand were selected. In the series by Bedfort and Wallman[15] 105 radial artery cannulations were prospectively studied in 100 patients. Forty (38%) radial arteries were occluded. No major ischemic complications were detected in these patients, but 4 patients had signs of distal vascular insufficiency in the form of a pale, cold thenar eminence. Mandel and Dauchot[16] reviewed 1000 radial artery cannulations. The cannulas were removed after 5 hours to 5 days. Distal ischemia requiring embolectomy or vascular reconstruction was encountered in only 2 (0.2%) patients. Slogoff et al.[17] examined 1699 patients who had prolonged radial artery cannulation for monitoring purposes after cardiac surgery. Although flow was diminished or absent in 25% of patients during Doppler examination, no ischemic damage or disability of the hand occurred. Based on our experience and on these reports, we consider radial artery cannulation as a low-risk entry site even if postprocedural radial artery patency is absent. The absence of puncture-related complications reduces the costs of coronary interventions by reducing the need for diagnostic procedures, the need for vascular surgery, and hospital stay (1.6 days in this study).

The high procedural and clinical success rate, the possibility of using bailout techniques such as perfusion balloons and coronary stents for treatment of suboptimal PTCA results, and the absence of major puncture site–related complications makes the radial artery an promising entry site for coronary angioplasty. To compare the safety and efficacy of this approach with those of the percutaneous femoral and brachial approach a randomized study is being performed in our department.

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CHAPTER 4.5.2

POTENTIAL SOLUTIONS

RADIAL ARTERY AS ENTRY SITE

Transradial coronary angioplasty

A RANDOMIZED COMPARISON OF CORONARY ANGIOPLASTY BY THE TRANSRADIAL, TRANSBRACHIAL OR TRANSFEMORAL APPROACH: INTERIM ANALYSIS OF THE ACCESS-STUDY

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A randomized comparison of coronary angioplasty by the transradial, transbrachial and transfemoral approach: Interim analysis of the ACCESS- study

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ABSTRACT

Background. Miniaturization of angioplasty material has made coronary angioplasty (PTCA) via the radial artery feasible.
No randomized data are available on procedural and clinical outcome of PTCA with 6F guiding catheters, introduced via the radial, brachial or femoral arteries.
Methods. To compare the mutual relation between access-failure rates and vascular complications, under the assumption that PTCA- results are equal, a randomized comparison is performed in our center between elective transradial, transbrachial and transfemoral PTCA with 6 French guiding catheters in 900 pts. Primary endpoints are entrysite related (necessity to puncture 2nd access-site, Hb-loss>2 mmol/l, transfusions, vascular interventions) and angioplasty related (death, CABG, rePTCA, MI, unstable angina, residual stenosis>50%).
Secondary endpoints are QCA- pre and postPTCA, vascular ultrasound findings, procedural and fluoroscopy time and hospitalization. An interim analysis at 450 pts was performed. Baseline characteristics were balanced in all groups.
Results. A successful coronary cannulation was achieved in 140 (92.1%), 141 (96.6%) and in 152 (100%) of patients, randomized to the radial, brachial and femoral artery respectively. In this order a successful PTCA procedure (with or without stenting) was achieved in 93.4%, 95.1% and 96.0% of patients (p=ns).
Procedural time (and as a consequence fluoroscopy time) of transradial PTCA was longer (43.7 ± 26.4; median 37 minutes) compared to transbrachial PTCA (40.6 ± 26.9; median 33) [p=ns] and transfemoral PTCA (36.6 ± 24.3; median 30) [p{radial-femoral}=0.02]. Cardiac events during hospital stay showed no significant differences in the three groups.
No ischemic complications of the hand were recorded following transradial PTCA, even in patients with absent radial artery pulsations (n=12; 7.8%) at discharge. No major entrysite related bleeding complications were encountered in this group, whereas 2 patients (1.3%) {p=ns} in the femoral group and 6 patients (4.1%) in the brachial group (p=0.03) had an access complication, requiring intervention. The mean hospital stay in the radial group was 1.5 ± 1.8 days (median 1; range 0-15) in the brachial group 1.6 ± 1.8 (median 1; range 1-12) and in the femoral group 1.7 ± 3.4 (median 1; range 0-39) [p=NS].
Conclusion: Procedural and clinical outcome of PTCA with 6F guiding catheters are favorable and similar for the three subgroups, but access- failure is more common during transradial PTCA. Bleeding complications are more frequently encountered after transbrachial angioplasty. The ACCESS-study will be continued to an enrollment of 900 patients.

INTRODUCTION

Safety of transradial coronary catheterization is mainly determined by the favourable anatomical relations of the radial artery to its surrounding structures. No major veins or nerves are located near the radial artery, excluding the chance of relevant injury of these structures. Because of the superficial course of the artery, hemostasis easily can be obtained by local compression. Thrombotic or traumatic artery occlusion does not endanger the viability of the hand, if adequate collateral blood supply from the ulnar artery is present. We modified the technique of transradial coronary catheterization as described by Campeau in 1989 (1), to perform transradial coronary angioplasty (PTCA), with 6 French (F) guiding catheters and minia-

turized balloncatheters. In 1992, when these catheters became commercially available, we initiated a feasibility study towards transradial artery coronary angioplasty (PTCA). In a series of 100 patients, PTCA could be performed via the radial artery in 94 patients; procedural success in this group was 98% (2). No major bleeding complications were encountered. Since little is known about the incidence of access failure and vascular complications after insertion of 6F guiding catheters in the femoral and brachial artery and since no randomized data are available comparing these three approaches, we designed the ACCESS-study: (A randomized Comparison of perCutaneous Entry SiteS for coronary angioplasty). This is an open, randomized, single center study, to establish the mutual relation of access-failure rates and vascular complications of transradial, transbrachial and transfemoral PTCA with miniaturized (6F) PTCA equipment under the assumption that PTCA results are equal in the three treatment groups. The total study will include 900 patients.
We describe the results of the interim analysis of procedural and clinical outcome, performed after enrollment of 450 patients.

METHODS

Patient selection

Patients were included with both stable and unstable angina, selected for single or multivessel PTCA of lesions in native coronary arteries and venous bypass grafts.
Suitability to participate in this study, concerning cardiac status, was assessed by one of the investigators. At arrival of the patient in the catheterization laboratory, femoral, brachial, radial and ulnar artery pulsations were examined and the Allen- test was performed. Informed consent of the patient to participate in this study was obtained if the patient fullfilled the enrollment criteria. Exclusion criteria are represented in Table 1.
If no exclusion criteria were encountered, the patients were randomized to the radial, brachial or femoral artery approach.

Medical preparation

At the start of the procedure patients received Diazepam 5 mg orally and Aspegic 900 mg intravenously. The puncture site was infiltrated with Xylocaine 2%, 2-10cc. Heparin 5.000 IU was administered via the introducer sheath at the start of the procedure.
After sheath removal and local hemostasis, heparin infusion was continued "overnight" in case of angiographical evidence of intracoronary thrombosis or dissection.
Nitroglycerin 100-300 microgram was administered before the first coronary angiogram and before the final angiogram and repeated if necessary.

Femoral and brachial cannulation

In all patients the percutaneous transluminal technique was used. After appearance of pulsatile blood from the arterial needle, an 0.035 inch guidewire was advanced, followed by insertion of a 6F arterial introducer, 10 cm in length.

Radial artery cannulation

The right arm, supported by an extension of the catheterization table is abducted (approximately 45^{o}) and the wrist is hyperextended.
After local anesthesia with Xylocaine 2%, the radial artery is punctured with an Arrow®, 22 GA Radial artery catheterization set or with an 18G arterial needle at 1 cm proximal from the styloid process. After appearance of pulsatile flow from the needle an Angiomed® 0.025 inch, 260 cm long guidewire is introduced through this system, followed by insertion of a 6 French, 23 cm long arterial introducer, after having made a small skin incision with a #11 surgical blade.

Table 1. Exclusion criteria

A. Vascular status.	
	Absence of pulsating femoral, brachial or radial arteries
	Absence of collaterals between radial and ulnar arteries (Negative Allen-test)
	Previous surgery at a potential entry site
	Failed previous attempts
B. Cardiac status	
	Chronic total occlusion
	Acute myocardial infarction
	Expected severe hemodynamic deterioration during balloon inflation or after PTCA- failure, leading to intraaortic balloon pumping or right heart catheterization for haemodynamic monitoring.
	Expected need for insertion of a temporary pacemaker
C. Procedural	
	Ad-hoc PTCA, following diagnostic coronary angiography
	Indwelling sheath from previous arterial punction
	Planned stent implantation
	Planned rotational or directional coronary atherectomy
C. General	
	No consent

Coronary artery cannulation
Six French guiding catheters were available from Scimed® (Inner diameter 0.060 inch), Schneider® (ID 0.061 inch) and from Cordis® (ID 0.062 inch). A 6 French guiding catheter was selected with an appropriate curve, providing maximal backup support during angioplasty. In all patients compliant rapid exchange balloon catheters were used (Scimed Express™) in combination with an ACS® 0.014 inch High Torque Floppy guidewire.

Access failure
After a failed attempt to cannulate the coronary artery, because of an access- site related problem, the operator was free to select any other entry- site. This could be the same artery at the contralateral side or any other artery. Selection of a second entry site to achieve a successfull angioplasty was considered to be a primary endpoint (Table 2).

Sheath removal, immobilization and discharge
In all instances, the arterial sheath was removed, directly after withdrawal of the guiding catheter, followed by application of a tourniquet at the radial puncture site or by manual compression of the brachial and femoral punture sites. A pressure bandage over the punctured artery was applied for 4 hours. After femoral entry, patients had bed rest for 6 hours. Following brachial and radial entry patients were not restricted to bed rest, but the patients were advised to restrict movements of elbow and wrist joint respectively. If no complications were encountered, the patient was discharged the day following PTCA.

Qualitative coronary analysis
Preprocedural lesion morphology was classified according to the definitions established by an American College of Cardiology/American Heart Association task force (3). Post- procedural coronary artery dissections were described according to the classification described by Dorros et. al.(4).

Quantitative coronary analysis
The x-ray imaging equipment used was the Philips Poly Diagnost C2, equipped with a Digital Cardiac Imaging system (DCI) (Philips Medical Systems, Eindhoven, the Netherlands). This system gives on-line video digitized images, for optimal angiographic assessment of coronary artery anatomy.
Quantitative analysis of coronary segments was performed with this system before and angioplasty and after the final balloon inflation under standardized conditions.

Assessments and examinations
An ECG was made before and after the procedure and at 1 month follow-up.
Laboratory assessments were hemoglobin and hematocrit before PTCA and at discharge and creatine phosphokinase (included MB- fraction) prior to discharge.
At discharge physical examination of the puncture site was performed on the presence of a complication (occlusion, hematoma, arteriovenous fisula, pseudoaneurysm) followed by a 2D and Doppler ultrasound examination.

Follow-up evaluation
One month after the procedure patients were examined at the outpatient clinic and screened for the presence of any access-site related and cardiac complication.

Endpoints
Primary access- site and PTCA related endpoints and secondary endpoints are shown in Table 2.

Table 2. Primary and secundary endpoints

A. PRIMARY ENDPOINTS
I. Access-site failure defined as either one of the following:
1. Necessity to puncture second access-site for any failure.
2. Access- site complication with: hemoglobin-loss ≥ 2 points and/or
blood transfusions and/or
vascular repair

II. PTCA- failure
1. Residual stenosis > 50% after (perfusion-) balloon angioplasty or stent implantation
2. Death
3. Myocardial infarction
4. Unstable angina pectoris
5. Need for coronary artery bypass grafting
6. Need for repeat PTCA

B. SECONDARY ENDPOINTS
1. Change in Minimal Lumen Diameter (and %diameter stenosis) pre- and post PTCA
2. Ultrasound findings: pseudoaneurysm, arteriovenous- fistula, occlusion, hematoma
3. Duration of the procedure
4. Fluoroscopy time
5. Consumption of angioplasty material
6. Hospital stay

Statistical analysis
Randomization was performed by opening of a closed envelope, containing a code for either

transradial (R), transbrachial (B) or transfemoral (F) angioplasty. These envelopes were ordered at random and provided of a registration number, running from 1 to 900.
Continuous variables are expressed as means ± SD and were compared by the unpaired two-tailed Student's t test. Proportions were compared with the Chi square test.
Statistical signifance was defined as $p < 0.05$. An interim analysis on an intention to treat basis was made after enrollment of 450 patients.

DEFINITIONS

Allen- test
Positive (normal) when after compression of both radial and ulnar arteries, a return of the normal colour of the hand occurs within 10 seconds after release of pressure over the ulnar artery.

Reversed Allen- test
Positive (normal) when after compression of both radial and ulnar arteries, a return of the normal colour of the hand occurs within 10 seconds after release of pressure over the radial artery.

Canadian Cardiovascular Society Classification
Class 0= Free of exertional angina
Class 1= No angina at ordinary physical activity
Class 2= Slight limitation of ordinary activity
Class 3= Marked limitation of ordinary activity
Class 4= Inability to carry on any physical activity without discomfort

Successful PTCA
Residual diameter stenosis postPTCA less than 50%, as assessed by QCA, irrespective the technique or device used after a having obtained a suboptimal result with conventional balloon angioplasty.

Major bleeding/catheter site complication
Any bleeding associated with a Hb- loss of 2 mmol/l or leading to blood transfusion, vascular repair or any complication leading to functional disability

Myocardial infarction
The presence of at least two of the following: 1. Occlusion of a previously patent coronary artery; 2. prolonged chest pain; 3. serial enzyme pattern typical for myocardial infarction, with at least one enzyme raised to more than twice the upper limit of normal; 4. the development of new Q- waves.

Repeat PTCA
PTCA after the guiding catheter has been removed out of the arterial sheath.

Bypass surgery
Emergency or elective coronary bypass surgery involving the previously dilated segment.

Cardiac death
All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established.

RESULTS

Study group

Between November 1993 and September 1994, 450 patients were included at our department; Radial artery group (R): n=152, Brachial artery group (B): n=146 and Femoral artery group (F): n=152. One patient included in the brachial and one in the femoral artery group was excluded from furher analysis, since at the time of the procedure, no significant lesion was present. Baseline clinical characteristics are displayed in Table 3. Angiographical and QCA-data are given in Tables 4 and 5. No significant differences were encountered between preprocedural variables in the three study subgroups.

Table 3. Baseline clinical characteristics

	RADIAL		BRACHIAL		FEMORAL		P
	n	(%)	n	(%)	n	(%)	
Male	114	(75.0)	105	(71.9)	115	(75.7)	NS
Age (year)	59.9 ± 10.9		60.8 ± 9.4		61.7 ± 11.1		NS
Height (cm)	174 ± 8		171 ± 8		173 ± 9		NS
Weight (kg)	79 ± 11		77 ± 11		79 ± 13		NS
CCS I	2	(1.3)	3	(2.1)	4	(2.6)	NS
CCS II	25	(16.4)	16	(11.0)	18	(12.0)	NS
CCS III	71	(46.7)	66	(45.2)	68	(44.7)	NS
CCS IV	40	(26.3)	46	(31.5)	49	(32.2)	NS
MI	60	(39.5)	63	(43.2)	70	(46.0)	NS
CABG	13	(8.5)	7	(4.8)	3	(3.3)	NS
PTCA	40	(26.3)	36	(24.7)	35	(23.0)	NS
Aspirin	129	(84.9)	110	(75.3)	119	(78.3)	NS
Coumadin	4	(2.6)	4	(2.7)	8	(5.3)	NS
Persantin	1	(0.7)	0	(0)	2	(1.3)	NS
Hypertension	46	(30.3)	51	(34.9)	45	(30.2)	NS
Diabetes	10	(6.6)	12	(8.2)	21	(13.8)	NS
Cholesterol	45	(29.6)	46	(31.5)	50	(32.9)	NS
Smoking	104	(68.4)	89	(61.0)	104	(68.4)	NS
Family	51	(33.6)	55	(37.7)	42	(27.6)	NS

CCS	Canadian Cardiovascular Society- angina pectoris classification
MI	Myocardial infarction
CABG	Coronary Artery Bypass Grafting
PTCA	Percutaneous Transluminal Coronary Angiography
NS	Not Significant

Table 4. Angiographical characteristics

	RADIAL		BRACHIAL		FEMORAL		P
	n	(%)	n	(%)	n	(%)	
No. Vessels	170	(100)	155	(100)	181	(100)	NS
LAD	76	(44.7)	73	(47.1)	74	(40.8)	NS
LCX	44	(25.9)	35	(22.6)	57	(31.5)	NS
RCA	45	(26.5)	42	(27.1)	46	(25.4)	NS
Other	5	(2.9)	5	(3.2)	4	(2.2)	NS
No. lesions	192	(100)	176	(100)	193	(100)	NS
Type*							
A	86	(44.8)	79	(44.9)	82	(42.5)	NS
B	70	(36.4)	55	(31.3)	64	(32.2)	NS
C	36	(18.8)	42	(23.8)	47	(24.3)	NS

LAD Left anterior descending coronary artery
LCX Left circumflex coronary artery
RCA Right coronary artery
*Reference #3

Table 5. Quantitative and qualitative coronary analysis

	RADIAL		BRACHIAL		FEMORAL		P
QCA- pre							
RD (mm)	2.66 ± 0.65		2.73 ± 0.67		2.66 ± 0.64		NS
MLD (mm)	0.80 ± 0.38		0.82 ± 0.45		0.77 ± 0.36		NS
DS (%)	69.8 ± 12.8		69.4 ± 15.5		71.0 ± 12.7		NS
QCA- post							
RD (mm)	2.76 ± 0.62		2.80 ± 0.58		2.77 ± 0.58		NS
MLD (mm)	2.09 ± 0.63		2.15 ± 0.69		2.12 ± 0.69		NS
DS (%)	24.0 ± 18.5		23.0 ± 16.0		23.9 ± 18.6		NS
Dissection							
Type*	N	(%)	N	(%)	N	(%)	
A	19	(12.5)	11	(7.6)	28	(18.5)	0.009**
B	24	(15.8)	30	(20.7)	29	(19.2)	NS
C	4	(2.6)	3	(2.1)	3	(2.0)	NS
D	0	(0)	0	(0)	3	(2.0)	NS
E	0	(0)	0	(0)	1	(0.7)	NS
F	4	(2.6)	1	(0.7)	1	(0.7)	NS
Total	51	(33.5)	45	(31.0)	65	(43.0)	0.04**

QCA Quantitative coronary analysis
RD Reference diameter
MLD Minimal luminal diameter
DS Diameter stenosis
*Reference #4
**Femoral-Brachial

Procedural results

Coronary cannulation

A successful coronary cannulation was achieved in 140 (92.1%), 141 (96.6%) and in 152 (100%) of patients, randomized to the radial, brachial and femoral artery respectively. In 12 patients from the radial group coronary cannulation failed versus none of the patients in the femoral group (p=0.001). In 5 pts from the brachial group, the coronary artery could not be reached (p=ns) because of a puncture failure (n=2), inability to advance the guidewire (n=1) or the guiding catheter (n=1). Most failures in the radial group were due to a puncture failure, whereas in 1 patient the sheath and in another the guidewire could not be advanced. During the same session, 11 patients crossed over to the femoral artery and 1 to the left radial artery, followed by a successful procedure. In the brachial artery group, 4 patients crossed over to the femoral artery and 1 to the radial artery, also with successful outcome.

Material consumption

In the radial and the brachial group, more guiding catheters (1.4 ± 1.0 and 1.3 ± 0.8 respectively) were used, compared to the femoral group (1.2 ± 0.5) [p=0.007 and p=0.03 respectively]. No differences were found in the number of guidewires and balloon catheters consumed (Table 6).

Table 6. Material consumption

	RADIAL	BRACHIAL	FEMORAL	P
	mean ± SD	mean ± SD	mean ± SD	
Guiding catheters	1.4 ± 1.0*	1.3 ± 0.8**	1.2 ± 0.5**/*	*0.007 **0.03
Guidewires	1.3 ± 0.7	1.2 ± 0.6	1.3 ± 0.9	NS
Balloon catheters	1.2 ± 0.6	1.2 ± 0.6	1.2 ± 0.5	NS

Coronary angioplasty

In the radial group 5 patients (3.3%) received a stent during the procedure to improve suboptimal balloon angioplasty results, in the brachial group 6 patients (4.3%) and in the femoral group 2 patients (1.3%) [p=ns]. A successful PTCA procedure (with or without stenting) was achieved in 93.4%, 95.1% and 96.0% of patients randomized to the radial, brachial and femoral approach, respectively (p=ns). Reasons for failed PTCA's (radial n=10 [6.6%]; brachial n=7 [4.9%] and femoral n=6 [4.0%]) and ensuing strategy are shown in Table 7. Results of final quantitative and qualitative coronary analysis post PTCA are given in Table 5. Compared to the patients in the brachial group, more dissections were seen in the femoral group. Thus 33.5%, 31.0% and 43.0% of patients in the radial, brachial and femoral groups were treated with a heparin infusion untill the next day.

Procedural time

Procedural time (moment from first attempt to puncture the artery to moment of sheath withdrawal) of transradial PTCA was longer (43.7 ± 26.4; median 37 minutes) compared to transbrachial PTCA (40.6 ± 26.9; median 33) [p=ns] and transfemoral PTCA (36.6 ± 24.3; median 30) [p{radial-femoral}=0.02].

Also, fluoroscopy time was longer; 13.7 ± 10.5: median 9.6, 13.0 ± 11.3: median 8.9 and 11.0 ± 10.2: median 6.9 minutes in the 3 groups respectively (p{radial-femoral}=0.02)

Table 7. Procedural outcome (intention to treat)

	RADIAL		BRACHIAL		FEMORAL		P
	n	(%)	n	(%)	n	(%)	
Unable to cross with							
-guidewire	5	(3.3)	4	(2.8)	3	(2.0)	NS
-balloon	3	(2.0)	0	(0)	1	(0.7)	NS
Final DS ≥50%	2	(1.3)	2	(1.4)	2	(1.3)	NS
Total	10	(6.6)	6	(4.2)	6	(4.0)	NS
Treatment							
-medically	6	(3.9)	3	(2.1)	3	(2.0)	NS
-rePTCA	2	(1.3)	0	(0)	1*	(0.7)	NS
-elective CABG	1	(0.7)	2	(1.4)	1	(0.7)	NS
-emergent CABG	0	(0)	1	(0.7)	1	(0.7)	NS
Procedural Success	142	(93.4)	138	(95.1)	145	(96.0)	NS

* *Successful LASER procedure for a total occlusion*

DS	Diameter stenosis
MI	Myocardial infarction
CABG	Coronary artery bypass grafting
PTCA	Percutaneous transluminal coronary angioplasty

Compression-time
Since no manual compression was applied over the radial artery, no man-power time was required to obtain hemostasis. No differences were recorded in manual compression time in the brachial artery (14.1 ± 8.3; median 12.2; range 3-55 minutes) and femoral artery group (12.8 ± 8.6; median 10.0; range 5-60 minutes).

Clinical course
Cardiac events
Cardiac events during hospital stay are shown in Table 8. No significant differences in the three groups were found. One patient died (Brachial group) from a intracerebral hemorrhage, during anticoagulation after bailout stent implantation. In the radial artery group, 2 patients underwent a second attempt via the femoral artery after a failure to cross the lesion; these were counted as a cardiac event.

Entrysite complications
No ischemic complications of the hand were recorded following transradial PTCA, even in patients with absent radial artery pulsations (n=12; 7.8%) at discharge. Spontaneous recanalisation was found in 4 of these patients, at 1 month follow-up. No major entrysite related bleeding complications were encountered in this group, whereas 6 patients (4.1%) in the brachial group (p=0.03) had an access complication, requiring intervention. Surgery was required in 3 patients (2 pseuaneurysms, 1 bleeding). One patient required bloodtransfusion. In one patient a pseudoaneurysm could successfully be obliterated by prolonged compression under ultrasonic guidance. One patient required local infiltration of analgetics for the treatment of nerve compression by a hematoma. In the femoral group, 2 patients (1.3%) required vascular surgery, one for a major bleeding and one for a pseudoaneurysm (p=ns).

Table 8. Cardiac events during hospital stay*

	RADIAL		BRACHIAL		FEMORAL		P
	n	(%)	n	(%)	n	(%)	NS
Death	0	(0)	1	(0.7)	0	(0)	NS
Q-wave MI	1	(0.7)	0	(0)	0	(0)	NS
Non-Q wave MI	2	(1.3)	1	(0.7)	1	(0.7)	NS
Emergent CABG	2	(1.3)	1	(0.7)	2	(1.3)	NS
Elective CABG	1	(0.7)	4	(2.8)	1	(0.7)	NS
Repeat PTCA	5	(3.3)	2	(1.4)	3	(2.0)	NS
Total	11	(7.2)	9	(6.4)	7	(4.7)	NS

* In the first collum, all events are taken into account, also multiple events in 1 patient (e.g. repeat PTCA, followed by emergent coronary bypass surgery and a non-Q wave myocardial infarction are counted as 3 separate events).

MI	Myocardial infarction
CABG	Coronary artery bypass grafting
PTCA	Percutaneous transluminal coronary angioplasty

Hospitalization

The mean hospital stay in the radial group was 1.5 ± 1.8 days (median 1; range 0-15) in the brachial group 1.6 ± 1.8 (median 1; range 1-12) and in the femoral group 1.7 ± 3.4 (median 1; range 0-39) [p=NS].

DISCUSSION

In this first half of the study, success rate of coronary cannulation via the radial artery was acceptable (92.1%). Most failures (n=10; 83.2%) were due to inability to puncture the radial artery. With better equipment selection and with improved experience, a better success rate can be achieved. Coronary cannulation was successful in 100% of the patients in the femoral group. This favorable outcome does not only reflect the operator's experience. Since patients with a previous failed catheterization, due to an entry-site problem, were excluded and since almost all patients had their diagnostic catheterization via the femoral artery, a bias towards a successful transfemoral catheterization was present. Once the radial artery was punctured, coronary catheterization was successful in 98.6%. More guiding catheters were used in the radial group and to a lesser extent in the brachial group, when compared to the femoral approach. This is explained by the fact that most guiding catheters are designed for the femoral approach; via the right arm the curves may have less adequate properties. Caused by a more difficult radial artery cannulation procedure and by problems with proper catheterselection and coronary cannulation, median procedural time and fluoroscopy time were longer compared to the femoral approach (7 and 2.7 minutes respectively; p=0.02). On the other hand, with the hemostasis techniques applied, no personel was involved to compress the radial artery, while manual compression of the brachial and femoral artery lasted 14.1 and 12.2 minutes, respectively.

No differences in procedural and clinical outcome of PTCA were present between the three groups. Procedural success rates with 6F guiding catheters were high; 93.4%, 95.1% and 96.0% for transradial, -brachial and -femoral PTCA, respectively. Only in 2 cases (0.4%) an attempt with 8F systems had to be undertaken, because lack of guiding catheter support was considered to be the main reason for failure; in 1 patient success was achieved. Since corona-

ry stenting has become an essential part of the PTCA- technique to improve suboptimal PTCA results (in this study 13 patients; 2.9%), it is important to notice 6F guiding catheters do not preclude the use of Palmaz Schatz coronary stents. The applicability of stents through 6F catheters has recently been reported (5,6,7,8,9). We also reported on the feasibility of applying perfusionballoons through 6F catheters in elective and in bailout situations (7,10). The main reason to start the percutaneous transradial PTCA program (2) was to abolish entry-site complications. Indeed, no major bleeding complications were encountered after transradial PTCA.
Early radial artery occlusion was encountered in 12 (7.8%) patients; spontaneous recanalisation was found in 4 patients. In the feasibility studies on transradial PTCA (100 pts) and on transradial stenting (100 pts), incidence of radial artery occlusion was also low (2,11) when compared to a 30% and 38% incidence of radial artery occlusion reported by Davis et al (12) and by Bedfort et al. (13), respectively, after prolonged cannulations of the radial artery for blood pressure monitoring. Symptoms and signs of radial artery occlusion were absent. In the series of Bedfort e.a. 105 radial artery cannulations were prospectively studied in 100 patients. Radial artery thrombosis was found in 40 patients (38%). No major ischemic complications were detected in these patients, but 4 patients had signs of distal vascular insufficiency, in the form of a pale, cold thenar eminence. Mandel e.a. reviewed 1.000 radial artery cannulations (14). The cannulas were removed after 5 hours to 5 days. Distal ischemia, requiring embolectomy or vascular reconstruction was encountered in only 2 patients (0.2%). Slogoff et.al. analysed 1.699 patients who had prolonged radial artery cannulation for monitoring purposes after cardiac surgery (15). Although 25% of patients had deminished or absent flow during Doppler examination, no ischemic damage or disability of the hand occurred in any patient. Thus the radial artery can be considered as a low risk entry site, even if post procedural radial artery patency is absent. Most complications were seen after transbrachial angioplasty. This may be due to the overlying tendon of the biceps muscle and to the relation of the brachial artery to its surrounding structures. Artery, vein and nerve are located near eachother. Thus arteriovenous fistula and nerve damage can result during attempts to puncture the artery. The brachial artery is more difficult to compress, especially if the upper arm is very muscular or obese. Finally, the elbow is more difficult to immobilize.

Study limitations. The bias towards a more favorable transfemoral catheterization success has been mentioned: exclusion of previous failures and the use of catheters, designed for the femoral approach. This partially explains the longer procedural and fluoroscopy times for the transradial- and brachial approaches. By using the left radial or brachial artery, the guiding catheter problem is solved. However, working from the left side of the patient, may be cumbersome. We have only limited experience with left radial procedures, performed at the right side of the patient. A suitable guiding catheter, specifically designed for the right radial approach may offer a solution.
The study will be continued to an inclusion of 900 patients.

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CHAPTER 4.6.1

POTENTIAL SOLUTIONS

RADIAL ARTERY AS ENTRY SITE

Transradial artery coronary stent implantation

PERCUTANEOUS TRANSRADIAL ARTERY APPROACH FOR CORONARY STENT IMPLANTATION

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Catheterization and Cardiovascular Diagnosis 30:173–178 (1993)

Percutaneous Transradial Artery Approach for Coronary Stent Implantation

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A new approach for implantation of Palmaz Schatz coronary stents is reported. We describe the technique and rationale of coronary stenting with miniaturized angioplasty equipment via the radial artery.

This technique is illustrated in three patients. One patient underwent Palmaz Schatz stent implantation for a saphenous vene coronary bypass graft stenosis, the second patient for a restenosis in the anterior descending coronary artery after atherectomy, and the third patient for a second restenosis after balloon angioplasty in the circumflex coronary artery.

Key words: Percutaneous transluminal coronary angioplasty, coronary stent

INTRODUCTION

Coronary stenting has been developed to overcome two major limitations of coronary balloon angioplasty (PTCA): abrupt closure and late restenosis. Agressive anticoagulant therapy is mandatory to prevent thrombotic occlusion of the stent.

Coronary stenting by the femoral artery approach carries a substantial risk for bleeding complications, especially if large-bore guiding catheters and arterial introducer sheaths are used. A possible solution for preventing severe puncture site-related events may be found in the combination of a smaller puncture opening with selection of another entry site. With the introduction of 6 French guiding catheters allowing passage of low-profile monorail balloon catheters, PTCA via the radial artery became possible. In an ongoing study exploring the feasibility of transradial artery coronary angioplasty, PTCA success via the radial artery was 90% in 50 patients (submitted). No vascular complications urged to bloodtransfusion or vascular surgery. Even in case of Doppler-proven radial artery occlusion (6%), no functional disability of the hand was reported. Encouraged by these results, we performed transradial artery Palmaz Schatz coronary stent implantation through 6F guiding catheters. This report describes the technique in three patients.

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TECHNIQUE

Patient Selection

In an ongoing study, patients undergoing stent implantation and having a good pulsating radial artery and a positive Allen test were selected for the transradial artery approach, irrespective of sex, weight, and size. The Allen test was considered positive when, after compression of both ulnar and radial arteries, a return of the normal colour of the hand occurred within 10 sec after release of the ulnar artery.

Medical Treatment

Patients are treated with Dextran 40, the first 500 ml at a rate of 100 ml/hr, the second 500 ml at a rate of 50 ml/hr. The infusion is started 2 hr before elective stent implantation or from the moment the decision is made to implant a stent in acute situations.

At the day of stent implantation, dipirydamole 225 mg/day and acetosalicylic acid 300 mg/d are started. After sheath insertion, 10.000 IU heparin is administered intra-arterially, followed by 5.000 IU for each hr the procedure lasts. Three hr after hemostasis is achieved, 3.000 IU heparin is administered intravenously. Heparin is titrated to Activated Partial Thromboplastin Times (APTTs) of 80–100 secs until stable adjustment on oral anticoagulant drug therapy (3 consecutive therapeutic Thrombotests). Coumadin is given for 3 mo and acetosalicylic acid and dipyridamole are given for 6 mos.

In order to prevent radial and coronary artery spasm, 10 mg nifedipine are administered sublingually.

Radial Artery Catheterization

The right arm is abducted to an angle of 70°, and the wrist is hyperextended.

After local anaesthesia with lidocaine 2%, the radial artery is punctured with an Arrow®, 22 GA Radial artery catheterization set at an angle of 45° at 1 cm proximal from the styloid process. After appearance of pulsatile flow from the needle an Angiomed® 0.025″, 260-cm-long guidewire is introduced through this system, followed by insertion of a Bard® Hemaquet II, 6 French 10-cm arterial introducer, after having made a small skin incision with a #11 surgical blade.

Coronary Artery Cannulation

A Scimed® 6 French guiding catheter (inner diameter 0.060", shaft length 100 cm) is selected with an appropriate curve, providing maximal backup support during angioplasty and stent implantation.

Angioplasty

After angiography an ACS® High Torque Floppy 0.014" guidewire is advanced across the lesion. Over this guidewire a rapid exchange, low profile, compliant balloon catheter (Scimed® Express) is positioned at the stenosis. This dilatation catheter can easily be advanced through 6 French guiding catheters, is easy to exchange, and has variable diameters, dependent on inflation pressures.

This inflation pressure-dependent variation of balloon diameter makes a single balloon approach for the complete procedure possible. The balloon size during predilatation corresponds to the reference diameter of the coronary artery. The stenosis is predilated in order to reduce friction between stent and lesion.

Stent Preparation

The predilating balloon catheter is used as stent carrier, because its increased profile after the first inflations will allow better support for the stent, compared to a balloon, tightly wrapped on the catheter shaft. The balloon is cleaned with saline to remove contrast agent, possible blood clots, and lubricating coating. A 7.3 mm (prefabricated) or 15 mm Palmaz Schatz coronary stent (Johnson and Johnson) is manually crimped on the balloon catheter, such that the balloon marker is positioned at the articulation site from the stent (15 mm) or in the middle of the stent (7 mm). No free movement from the stent over the balloon is allowed to persist.

Stent Delivery

The stent-loaded balloon catheter is advanced over the guidewire toward the stenosis, under concomitant contrast delivery. The articulation site of the Palmaz Schatz stent, the weakest portion of the stent, is positioned just eccentric from the narrowest part of the stenosis. After delivery, the stent diameter is optimized by successive dilatations with larger balloon catheters or higher inflation pressures.

Introducer Sheath Removal, Hemostasis, and Heparinization

The arterial sheath is removed immediately after the procedure. Hemostasis is achieved by progressively decreasing compression with a tourniquet over the puncture site during 30–45 mins. This is followed by application of a pressure dressing during 6 hr. The patient is free to mobilize.

RESULTS

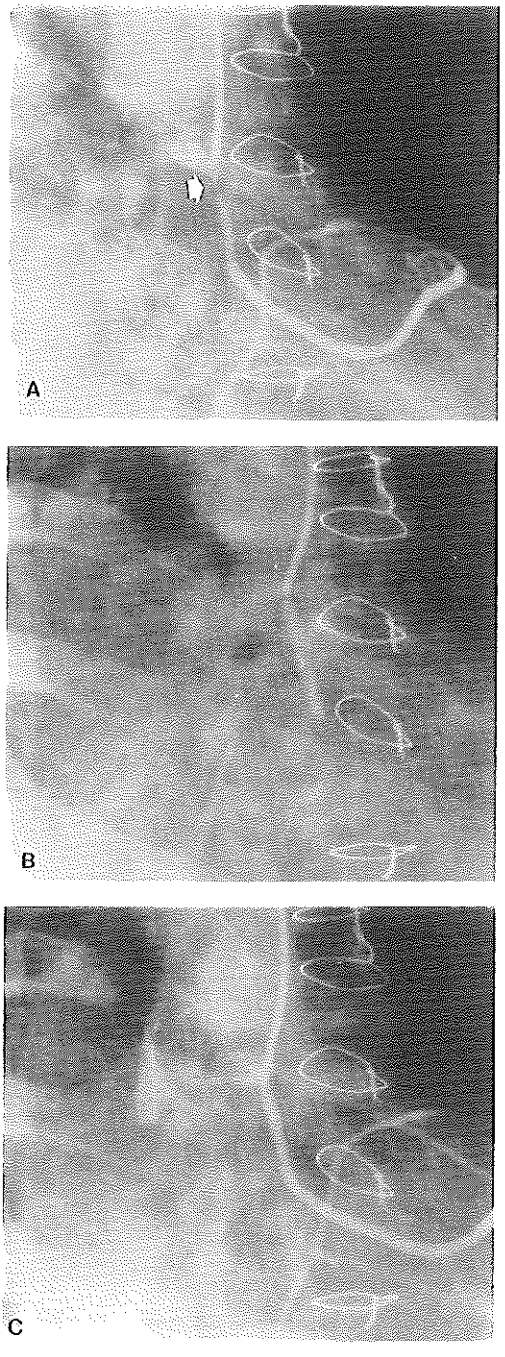
Patient 1

A 71-year-old male with a history of coronary artery bypass surgery in 1988 for stable angina pectoris and triple coronary artery disease was admitted to our department for recent onset anginal attacks. Cardiac catheterization revealed severe triple vessel disease and a significant stenosis proximal in a saphenous vene jump graft, with anastomoses on the first diagonal, obtuse marginal, and on the posterolateral and descending posterior branches of the right coronary artery (Fig. 1A). This culprit lesion was considered suitable for angioplasty and primary implantation of a Palmaz Schatz coronary stent. The presence of collaterals between a well-developed right radial artery and ulnar artery, as demonstrated by the Allen test, allowed a transradial artery approach. Over the guidewire a Scimed® 6 French multipurpose II guidingcatheter was advanced to the ostium of the venous bypass graft, followed by visualization of the lesion. Quantitative coronary analysis (Philips Digital Coronary Imaging; Philips Medical Systems, Best, The Netherlands) revealed a stenosis > 8 mm in length, extending from the ostium of the bypass graft (minimal luminal diameter [MLD] 1.04 mm, reference diameter [RD] 3.05 mm, diameter stenosis [DS] 66%). Predilatation with 2 inflations at 6 atmospheres during 120 sec with a Scimed® Express 2.5 mm balloon catheter reduced the stenosis to < 50%. After adequate positioning, a 15 mm long stent was delivered with the same dilatation catheter being inflated with 12 atmospheres during 30 sec (Fig. 1B).

The result was optimized by repeat dilatations with 3.0 and 3.5 mm Scimed® Express balloons, resulting in an 17% residual stenosis (MLD 2.7 mm, RD 3.26 mm) (Fig. 1C). The clinical course was uncomplicated. Physical, 2-dimensional and Doppler ultrasound examinations of the right radial artery were normal. Patient was discharged 6 days after stent implantation.

Patient 2

A 48-year-old man was admitted for unstable angina pectoris and ST-segment elevation in the precordial leads. Cardiac enzymes did not rise and a diagnostic catheterization, 1 d after admission, showed a normal left ventricular function and a significant stenosis proximal in the left anterior descending coronary artery (LAD) (Fig. 2A). One wk later we performed a successful directional atherectomy with a 7 French Simpson Coronary Atheterocath (DVI) (Fig. 2B,C). Two mo later, the patient was readmitted with unstable angina. A



significant restenosis in the proximal LAD (Fig. 2D) was considered suitable for Palmaz Schatz stent implantation. A patent radial artery and collateral blood supply of the hand allowed a transradial artery approach. A Scimed® Amplatz Left II 6 French guiding catheter provided optimal support for angioplasty. With quantitative coronary angiography the lesion showed to be 10 mm in length (MLD 0.58 mm, RD 2.79 mm, DS 71%). Predilatation with a 3.0 mm balloon at 4 atmospheres during 45 secs significantly reduced the stenosis. The stent was crimped on the same balloon and successfully delivered at 10 atmospheres during 40 sec (Fig. 2E). The angiographical result was optimized with one dilatation at 12 atmospheres. Quantitative angiography revealed an 11% stenosis at the articulation site (MLD 2.98 mm, RD 3.34 mm) (Fig. 2F).

The sheath was removed directly after the last contrast injection, and hemostasis was obtained after 45 mins. Physical, 2-dimensional, and Doppler ultrasound examination of the radial artery revealed no abnormalities. The subsequent clinical course was uneventful, and patient was discharged 7 d after stent implantation.

Patient 3

A 63-year-old man with previous successful PTCA of the LAD (1989) and first diagonal branch of the LAD (1991) was admitted in October 1992 with unstable angina. Coronary angiography showed good long-term PTCA result of the LAD and first diagonal branch and a significant stenosis in the proximal segment of the ramus circumflexus (RCX), which was successfully reduced by balloon angioplasty. Because of progressive anginal complaints, patient underwent repeat PTCA of a significant restenosis in the RCX 3 mos later. After 1 mo, the patient was readmitted for unstable angina. Because a second restenosis in the RCX was suspected to be responsible for the patient's complaints, stent implantation was planned directly after diagnostic angiography.

After medical preparation for coronary stenting, coronary angiography was performed via the right radial artery with a 6 French Scimed® Amplatz Left I guiding catheter. This indeed revealed a 77% restenosis in the RCX (MLD 0.74 mm, RD 3.17 mm) (Fig. 3A). The lesion was predilated with a Scimed® Express 2.5 mm balloon catheter at 12 atmospheres during 120 secs. On a 3.0 mm balloon catheter, a 15 mm Palmaz Schatz stent was manually fixed. The stent was delivered with 13 atmospheres. Despite one more dilatation with a 3.5 mm

Fig. 1. A. Proximal stenosis (arrow) extending from ostium of the venous bypass graft. B. Stent delivery with a Scimed® Express 2.5 mm balloon catheter at 12 atmospheres. C. Final result.

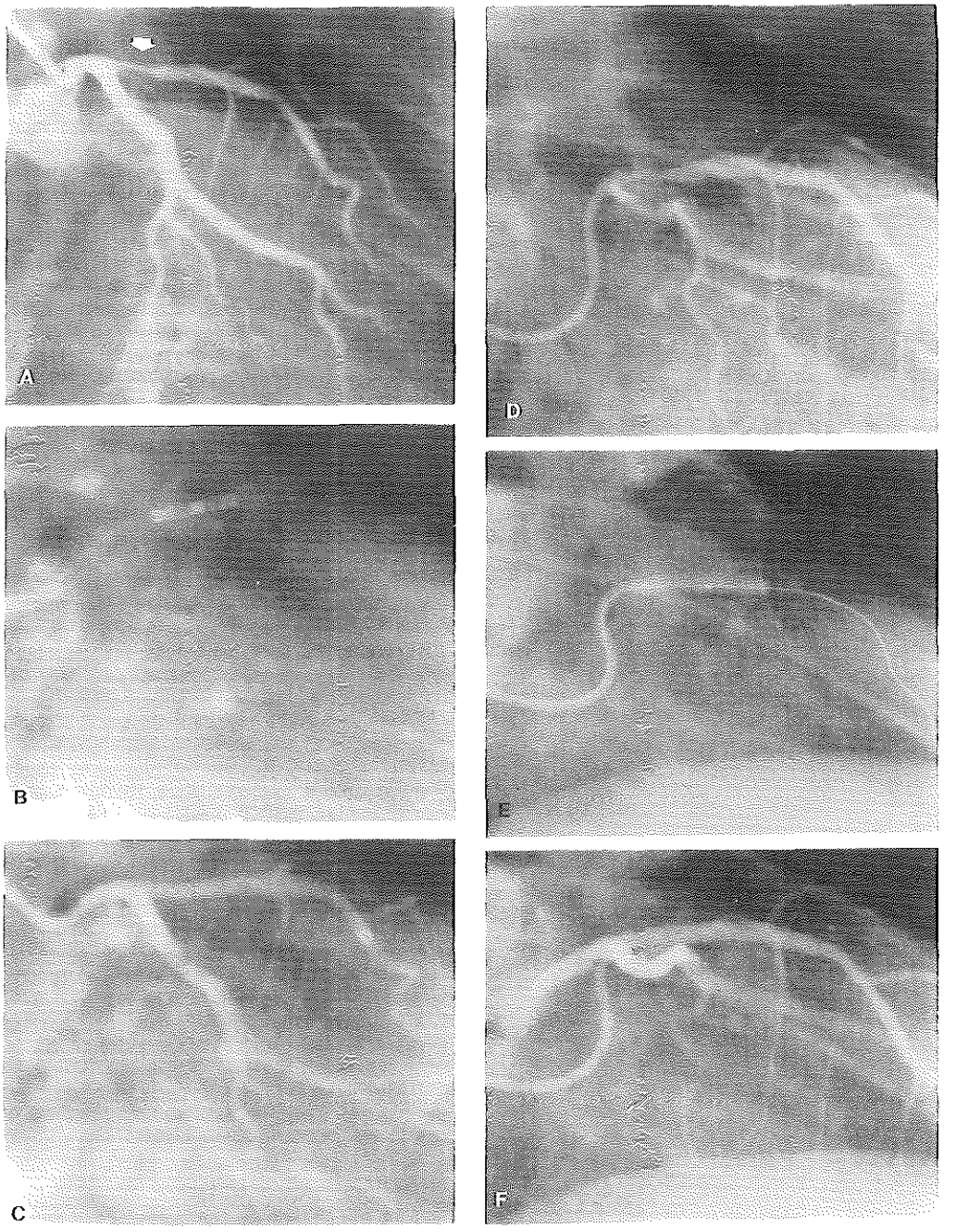


Fig. 2. A. Proximal stenosis (arrow) in the left anterior descending coronary artery. B. Directional atherectomy with a 7 French Simpson Coronary AtheroCath. C. Immediate result after directional atherectomy. D. Proximal restenosis in the LAD. E. Stent delivery with Scimed® Express 3.0 mm balloon catheter at 10 atmospheres. F. Final result.

balloon at 10 atmospheres (Fig. 3B), a 33% stenosis persisted (MLD 2.47 mm, RD 3.65 mm) (Fig. 3C). The sheath was removed immediately after the procedure, and hemostasis was obtained after 30 minutes.

The hospital course was uneventful and patient was discharged 1 wk after the procedure.

DISCUSSION

The main concern after implantation of metallic coronary stents is to find an optimal balance between hemostasis and anticoagulation. The incidence of puncture site-related bleeding complications after coronary stenting has been reported to vary between 7.9% of 226 patients in the initial multicenter experience with the Palmaz Schatz stent [1] and 16% of 220 patients in single center experience with the Gianturco-Roubin stent [2]. A bleeding complication does not only have serious local sequelae, but it may also force this balance toward suboptimal heparinization, with increased risk of stent occlusion.

A possible solution for preventing severe puncture site-related events may be found in the combination of a smaller puncture opening with selection of another entry site. In recent years development of miniaturized PTCA equipment allowed the use of 7 French (3), 6 French [4,5], and even 4 French [6] guiding catheters for coronary angioplasty.

Transfemoral artery stent implantation through 6 French guiding catheters has been reported in 3 patients by Urban et al. [7].

Dorros et al. [8] described an alternative route for performing percutaneous transluminal coronary angioplasty by performing arteriotomy of the brachial artery. At present there is extensive experience with percutaneous transbrachial coronary catheterization and angioplasty, showing to be an effective and safe alternative to the Sones- technique and the Seldinger- technique of the femoral artery [9–11].

Complications after brachial artery puncture are rare, but if present, they often require surgical repair [12]. Complications described are arteriovenous fistulae, nerve injury, thrombotic artery obstruction, dissection, and false aneurysm.

Campeau [12] reported on percutaneous entry of the radial artery for cardiac catheterization in 100 pts with a collateral blood supply to the hand. An arterial sheath, with an internal diameter of 5 French was used [12]. Only 2 symptomless, vascular complications were ob-

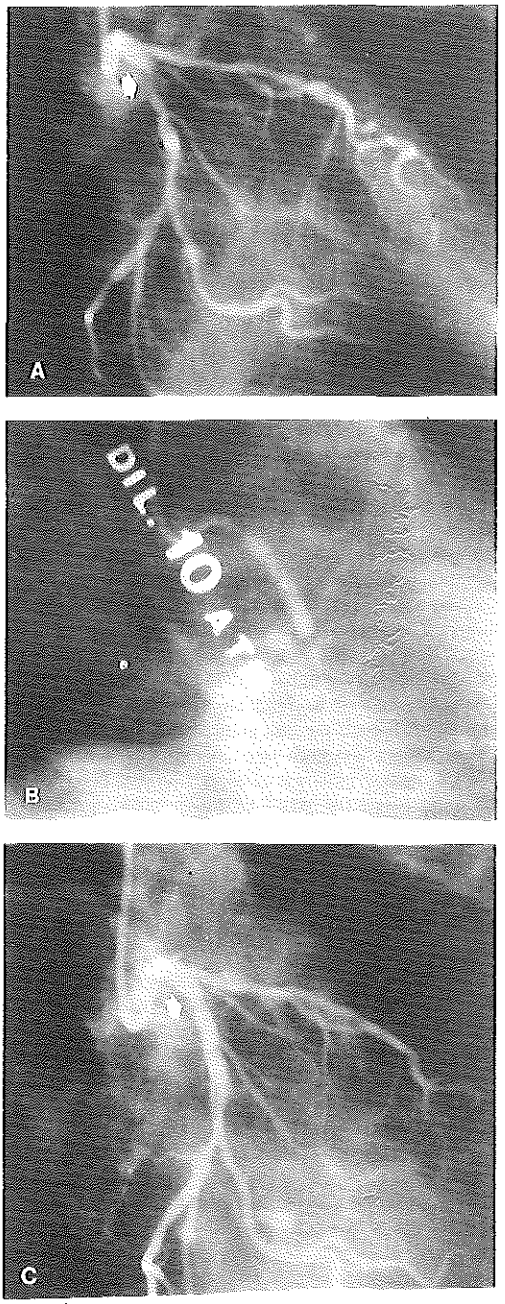


Fig. 3. A. Proximal restenosis (arrow) in the left circumflex coronary artery. B. Stent dilatation with Scimed® Express 3.5 mm balloon catheter at 10 atmospheres. C. Final result. Note residual stenosis (arrow).

served. Safety of transradial artery coronary catheterization is mainly determined by the favourable anatomical relations of the radial artery to its surrounding structures and the double blood supply to the hand. The sequelae of radial artery obstruction are frequently mild even in patients not selected for good collateral circulation. Slogoff et al. [13] reported on a series of 1,699 patients undergoing heart surgery, with perioperative radial artery cannulation. No ischemic damage to the hand was observed, even in 25% of patients with abnormal Doppler flow patterns, compatible with partial or complete radial artery occlusion [13]. No major veins or nerves are located near the radial artery, excluding relevant injury of these structures. Because of the superficial course of the artery, haemostasis easily can be obtained by local compression, which is of major importance. An additional advantage is the immediate ambulation of the patient, increasing comfort of the procedure. We recently explored the feasibility of transradial artery coronary angioplasty (submitted). PTCA success via the radial artery was 90% in 50 patients and no vascular complications urged to bloodtransfusion or vascular surgery. Radial artery occlusion (3 patients; 6%) was not associated with functional disability of the hand.

As illustrated in these cases, transradial artery stent implantation is feasible through 6 French guiding catheters. However, several theoretical limitations of this approach should be emphasized. As prefabricated, sheath-protected stent delivery systems cannot be advanced through 6 French guiding catheters, some risk for stent dislodgement and embolization exists, when the stent-loaded balloon passes the catheter lumen. Friction may shear the bare stent from the balloon, possibly leading to stent embolization. Therefore it is advised to crimp the stent on a balloon after it has been inflated several times in order to increase balloon profile, allowing better support to carry the stent. Removing the lubricating coating from the balloon may also help to keep the stent fixed to the balloon.

Small guiding catheters may provide less support than large ones. Adequate backup support is needed to allow passage of a metallic stent on an unlubricated balloon catheter beyond a coronary stenosis. For this reason, a guiding catheter curve has to be selected, which gives optimal support. We recommend to predilate a tight stenosis, because this will allow easier passage of the stent.

Visualization by contrast injection was satisfactory in these patients, allowing precise positioning of the stent in relation to the vascular segment of interest. However, in those situations requiring additional visualization techniques, such as angioscopy or intravascular ultrasound, large bore catheters are preferred.

Despite these limitations, when appropriate precautions are taken, transradial artery stent implantation may be a promising approach for a careful selected group of patients.

To explore the feasibility, safety, and efficacy of elective percutaneous transradial coronary Palmaz Schatz stent implantation with miniature angioplasty equipment in patients with symptomatic coronary artery disease, a prospective study is presently performed in our department.

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CHAPTER 4.6.2

POTENTIAL SOLUTIONS

RADIAL ARTERY AS ENTRY SITE

Transradial artery coronary stent implantation

PERCUTANEOUS TRANSRADIAL ARTERY APPROACH FOR CORONARY PALMAZ SCHATZ STENT IMPLANTATION

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Percutaneous transradial artery approach for coronary Palmaz-Schatz stent implantation

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The first metallic coronary stents were implanted in human beings in 1986 to overcome two major limitations of percutaneous transluminal coronary balloon angioplasty (PTCA): abrupt closure and late restenosis.[1] Rigorous anticoagulant therapy is mandatory to prevent thrombotic occlusion of metallic stents.[2] Coronary stenting by the femoral artery approach carries a substantial risk of bleeding complications, especially if large-bore guiding catheters are used. A possible prevention of severe puncture site–related events is the combination of a smaller puncture opening with selection of another entry site. With the introduction of 6F guiding catheters that allow passage of low-profile balloon catheters, percutaneous balloon angioplasty via the radial artery became possible as demonstrated by our group in 100 consecutive patients.[3] This report describes the technique, procedural results, and clinical course in 20 consecutive patients who underwent Palmaz Schatz coronary stent implantation via the radial artery.

METHODOLOGY

Patient selection. In an ongoing study, patients selected for coronary stent implantation who had a good pulsating right or left radial artery and a positive Allen test result were selected for transradial artery approach, irrespective of the patient's sex, weight, and size. The Allen test result was considered normal when, after compression of both ulnar and radial arteries, hand color returned to normal within 10 seconds after release of the ulnar artery. Patients were included in our study after giving informed consent.

Medical treatment. Patients were treated with Dextran 40, the first 500 ml at a rate of 100 ml/hr and the second 500 ml at 50 ml/hr. The infusion was started 2 hours before elective stent implantation or from the moment the decision was made to implant a stent in acute situations. At the day of stent implantation, dipyridamole 225 mg/day and acetosalicylic acid 300 mg/day was started. After sheath insertion, 10,000 IU of heparin was administered intraarterially, followed by 5,000 IU for each hour the procedure lasted. Three hours after hemostasis was achieved, 3,000 IU heparin was administered intravenously. Heparin was titrated to Activated Partial Thromboplastin Times (APTTs) of 80 to 100 seconds until stable adjustment on oral anticoagulant drug therapy (three consecutive therapeutic Thrombotests). Coumadin was given for 3 months and acetosalicylic acid and dipyridamole were given for 6 months. To prevent radial and coronary artery spasm, 10 mg nifedipine was administered sublingually before radial artery puncture.

Radial artery catheterization. The right arm was abducted to an angle of 70 degrees, and the wrist was hyperextended. After local anesthesia with lidocaine 2%, the radial artery was punctured with an Arrow (Arrow International, Reading, Pa.) 22-gauge radial artery catheterization set or an 18 gauge introducer needle at a 45-degree angle 1 cm proximal from the styloid process. After appearance of pulsatile flow from the needle, and Angiomed (Angiomed, Karlsruhe, Germany) 0.025-inch, 260 cm long guide wire was introduced through this system, followed by insertion of a Bard Hemaquet (Bard, Billerica, Mass.) II 6F 10 cm arterial introducer after a small skin incision was made with a No. 11 surgical blade.

Coronary artery cannulation. A Scimed Triguide (Scimed Life Systems, Maple Grove, Minn.) 6F

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guiding catheter (inner diameter 0.060 inch, shaft length 100 cm) was selected with an appropriate curve, providing maximal back-up support during angioplasty and stent implantation.

Angioplasty. After angiography an ACS (Advanced Cardiovascular Systems, Santa Clara, Calif.) High-Torque Floppy 0.014-inch guide wire was advanced across the lesion. Over this guide wire a rapid-exchange, low-profile, compliant balloon catheter (Scimed Express) was positioned at the stenosis. This dilatation catheter can easily be advanced through 6F guiding catheters, is easy to exchange, and has variable diameters depending on inflation pressures. This inflation pressure–dependent variation of balloon diameter makes a single-balloon approach possible for the complete procedure. The stenosis was predilated to facilitate positioning of the stent-loaded balloon at the lesion. Performance of the guiding catheter (back-up support, opacification, and pressure monitoring) and of the balloon catheter (crossability and retrievability) were semiquantitatively scored in three categories; good, moderate (sufficient; no need to change guiding or balloon catheter), and poor (suboptimal; need to change guiding or balloon catheter).

Stent preparation. The predilating balloon catheter was preferably used as stent carrier, because its increased profile after the first inflations allow better fixation for the stent compared to a balloon tightly wrapped on the catheter shaft. The balloon was cleaned with saline solution to remove contrast agent, possible blood clots, and lubricating coating. A 7.3 mm or 15 mm Palmaz-Schatz coronary stent (Johnson and Johnson Interventional Systems, Warren, N. J.) was manually crimped on the balloon catheter so that the balloon marker was positioned in the middle of the stent and no free movement from the stent over the balloon was noted.

Stent delivery. The stent-loaded balloon catheter was advanced over the guide wire toward the stenosis under concomitant contrast medium delivery. The articulation site of the 15 mm Palmaz-Schatz stent, the weakest portion of the stent, was positioned just eccentric from the site with the minimal luminal diameter. After delivery the stent diameter was optimized by successive dilatations with higher inflation pressures or larger balloon catheters.

Introducer sheath removal and hemostasis. In all instances the arterial sheath was removed immediately after withdrawal of the guiding catheter, followed by application of an occlusive tourniquet at the radial puncture site for a minimum of 30 minutes. Pressure was gradually released until hemostasis was obtained. A pressure bandage over the punctured artery was applied for 6 hours. Patients were not restricted to bed rest and were advised to restrict movement of the wrist joint.

Quantitative coronary analysis. The x-ray imaging equipment used was the Philips Poly Diagnost C2, equipped with a digital cardiac imaging (DCI) system (Philips Medical Systems, Eindhoven, The Netherlands). This system gives on-line video digitized images, for optimal angiographic assessment of coronary artery anatomy. Quantitative analysis of coronary segments was performed with this system before angioplasty and after the stent implantation or after the last balloon inflation within the coronary stent.

Predischarge examinations. The radial artery was controlled for the presence of pulsations, and the Allen test and reversed Allen test were repeated. Claudication of the hand was tested by having the patients open and close their hand 50 times. A two-dimensional and Doppler ultrasound study was performed before discharge.

Statistics. All values are expressed as mean ± SD.

OBSERVATIONS

Study population. Between March and June 1993 in 20 consecutive patients transradial artery implantation of a Palmaz Schatz stent was attempted for saphenous vein coronary bypass stenosis ($n = 9$, 45%), native coronary artery restenosis after previous angioplasty ($n = 7$, 35%) and for suboptimal PTCA results ($n = 4$, 20%). Twenty-five stents were implanted for 24 lesions in 20 vessels. During this episode two patients underwent coronary stent implantation via the femoral artery because this approach was required to participate in a multicenter randomized study in which stent implantation and balloon angioplasty (Benestent study) were compared. One patient had a transfemoral stent implantation immediately after transfemoral artery PTCA complicated by a coronary dissection. Patient baseline clinical characteristics are shown in Table I.

Angiographic data. Vessel distribution, TIMI grade flow, and type of lesion are summarized in Table II. Quantitative coronary angiographic data are listed in Table III.

Procedure

Radial artery cannulation. The radial artery was successfully punctured and cannulated within 15 minutes in all patients (85% within 5 minutes). No complications were encountered.

Guiding-catheter selection and performance. Coronary artery cannulation with 6F guiding catheters was successful within 15 minutes in 85% of the procedures (65% within 5 minutes). Thirty-nine guiding catheters were used (1.95 catheters/procedure). An

Table I. Baseline characteristics

No. of patients	20
Gender	
Male	16 (80%)
Female	4 (20%)
Age (yr)	
Mean ± SD	63 ± 12
Range	40-82
Height (cm)	
Mean ± SD	175 ± 7
Range	165-187
Weight (kg)	
Mean ± SD	86 ± 11
Range	70-106
Oral anticoagulation	
Acetyl salicylic acid	
No.	19
%	95
Dipyridamol	
No.	5
%	25
Coumadin	
No.	11
%	55
Exertional angina	
CCS III	
No.	9
%	45
CCS IV	
No.	8
%	40
Nonexertional angina	
No.	3
%	15
Mixed angina	
No.	8
%	40
Prior myocardial infarction	
No.	9
%	45
Prior bypass surgery	
No.	10
%	50
Hypertension	
No.	6
%	30
Diabetes mellitus	
No.	1
%	5
Cholesterol ≥6.5 mmol/L	
No.	3
%	15
Cigarette smoker	
No.	7
%	35
Family history	
No.	7
%	35
Disease	
Single-vessel	
No.	10
%	50
Two-vessel	
No.	1
%	5
Three-vessel	
No.	9
%	45

overview of guiding catheters used for stent implantation is given in Table IV. For these catheters, contrast opacification and pressure monitoring were rated as being good in all instances. Back-up support was moderate in 6 (30%) cases. Seven patients (35%) had discomfort in the arm during catheter manipulation. Additional application of nifedipin and local warm compresses was necessary in 4 (20%) patients.

Balloon-catheter selection and performance. Thirty-eight balloon catheters were used for 20 patients (1.9 balloons per patient). Details on predilatation, stent delivery, and oversizing are summarized in Table V.

Predilatation. In all but one elective procedure the lesions were predilated. Crossability through the guiding catheter and the target vessel was rated as being good in 89% and moderate in 11% of cases, but all balloons could be successfully positioned across the stenosis. All balloon catheters were easy to retract. After predilatation of a stenosis in the LAD, a major diagonal branch occluded in one patient; it remained occluded during the procedure and after stent implantation and resulted in a non-Q myocardial infarction (creatine phosphokinase-MB 64 mmol/L).

Stent delivery. Twenty-five stents (4 stents of 7.3 mm and 21 stents of 15 mm in length) were successfully implanted (1.25 stents per patient). Crossability through the guiding catheter and coronary artery was good during 21 implantations. Noticeable friction between the stent and the tip of Amplatz-shaped (left and right) guiding catheters was noticed in two patients, but the friction did not lead to stent dislodgement.

In one patient the guiding catheter (Judkins Left 4) did not provide enough support to advance a 7.3 mm stent at the target lesion in the LAD. In our attempt to withdraw the stent within the guiding catheter, we noticed displacement of the stent toward the distal end of the balloon. This stent was partially deployed in the LAD proximal from the target lesion and could not be crossed by the same stent delivery catheter. With a 2.0 mm balloon catheter, this stent could be expanded, followed by optimal deployment

Table II. Angiographic data.

No. of stents placed (n = 25)	
LAD	
No.	10
%	40
RCA	
No.	3
%	12
LCX	
No.	2
%	8
VBG	
No.	10
%	40
TIMI grade (20 vessels)	
0	
No.	1
%	5
1	
No.	1
%	5
2	
No.	1
%	5
3	
No.	17
%	85
Type (24 lesions)	
A	
No.	13
%	54
B	
No.	6
%	25
C	
No.	5
%	21

LAD, Left anterior descending coronary artery; *LCX*, left circumflex coronary artery; *RCA*, right coronary artery; *TIMI*, thrombolysis In Myocardial Infarction study; *VBG*, venous bypass graft.

Table III. Quantitative coronary angiography

	Baseline		*After stenting*	
	Mean ± SD	*Range*	*Mean ± SD*	*Range*
Reference diameter (mm)	3.2 ± 0.5	2.2-4.2	3.4-0.5	2.3-4.5
Minimal lumen diameter (mm)	0.9 ± 0.4	0-1.7	3.1 ± 0.4	2.4-4.1
Diameter stenosis (%)	71 ± 12	52-100	13 ± 10	0-32

Table IV. Selected guiding catheters (n = 20)

Curve	*n*	*%*
Judkins left	5	25
El gamal	5	25
Multipurpose	5	25
Amplatz left	3	15
Amplatz right	1	5
Judkins right	1	5

with a 3.5 mm balloon catheter. With the use of an Amplatz Left II guiding catheter, the target lesions were successfully stented. In another patient friction was noticed between the stent and the target lesion (LAD dissection). However, two stents were successfully implanted to cover the entire lesion. All other procedures were uncomplicated.

Opacification of the vessel containing the deflated, stent-loaded balloon easily allowed adequate positioning of the stent in relation to the culprit lesion. In eight patients no additional dilatations were applied after stent delivery because the angiographic result was considered optimal.

Oversizing. In four patients the stent was dilated at higher inflation pressures with the same balloon catheter to optimize the angiographic result. In eight patients stent deployment was improved by dilatations with a larger balloon. In one patient undergoing stent implantation for an obstructive dissection of the circumflex coronary artery after PTCA, three balloon catheters could not cross a well-deployed stent in the LCX to improve a residual dissection distal from the stent. With aggressive anticoagulation, this patient had an uncomplicated clinical course. Oversizing the stented segment with a larger balloon catheter was associated with the appearance of a dissection distal from a tandem stent in the LAD in the patient described earlier. In this segment a fourth stent was successfully implanted.

Angiographic results. All stents were angiographically well deployed (stent/coronary artery reference diameter ≥1 and no filling defects within the stent). Quantitative analysis data are summarized in Table V. In 2 (10%) patients some contast medium remained visible parallel to the vessel outside the stent. The patient with a small filling defect in the LCX just beyond the stent and the patient with sidebranch occlusion were described earlier.

Hemostasis. The arterial sheath was removed immediately after the last control angiogram. Hemostasis was obtained after 32 ± 11 minutes (range 20 to 60). In one patient some collagen (Vasoseal) was successfully applied subcutaneously near the puncture opening to stop prolonged bleeding.

Clinical course. All patients were free from acute or subacute stent thrombosis. Except for the patient with a non-Q myocardial infarction caused by occlu-

Table V. Inflation characteristics during predilatation, stent delivery, and oversizing

	Predilatation	*Stent delivery*	*Oversizing*
n	19	25	18
Balloon diameter (mm)			
2.0			
No.	1	—	—
%	5		
2.5			
No.	3	2	—
%	16	8	
3.0			
No.	9	13	5
%	47	52	33
3.5			
No.	6	10	7
%	32	40	47
4.0			
No.	—	—	3
%			20
Inflations (No.)			
Mean ± SD	1.5 ± .8	1.1 ± .3	1.2 ± .6
Range	1-4	1-2	1-3
Pressure (atm)			
Mean ± SD	8.4 ± 3.1	11.2 ± 1.7	10.2 ± 1.4
Range	4-13	8-14	8-12
Duration (sec)			
Mean ± SD	89 ± 50	55 ± 29	62 ± 30
Range	30-240	15-140	15-130
Size (mm)*			
Mean ± SD	3.2 ± .4	3.6 ± .3	3.7 ± .3
Range	2.3-4.1	3.0-4.1	3.2-4.2

*Manufacturer-specified balloon diameters at variable inflation pressures.

sion of a diagonal branch, no cardiac events were recorded. No bleeding complications leading to prolonged hospitalization, blood transfusion, vascular surgery, or functional disability were encountered. In five patients removal of the pressure dressing was followed by prolonged oozing of blood from the puncture site. When a new pressure dressing was applied bleeding could be stopped. Blood loss was minimal and did not require transfusion or surgical intervention.

No other clinical catheter site-related complications were encountered. One patient had temporary macroscopic hematuria during heparinization and adjustment on coumadin. No underlying cause could be detected, and blood transfusion was not required. Hospitalization was prolonged by 1 month in one patient requiring intravenous antibiotic treatment of a fever and *Staphylococcus aureus* bacteremia related to a contaminated intravenous cannula. The other patients were hospitalized for 6.1 ± 2.3 days (range 1 to 10, median 6 days) after stent implantation.

Doppler and physical radial artery studies. In all patients the radial artery was palpable at discharge. The reversed Allen test results were normal (after compression of both radial and ulnar arteries, hand color returned to normal within 10 seconds after release of the radial artery) in all patients. Claudication of the hand could not be provoked. Doppler ultrasound examination proved the presence of flow at the puncture site in all patients. In one patient a small hematoma and intima defect was visible on two-dimensional echography.

COMMENTS

Coronary stent implantation is currently used as a modality to improve results of percutaneous transluminal coronary balloon angioplasty (PTCA). The main concern after implantation of metallic coronary stents is prevention of stent thrombosis. The incidence of stent thrombosis is high, especially after stent implantation for abrupt coronary closure after PTCA.[4-7] A poststenting regimen of a combination of coumadin, heparin, dextran, acetosalycilic acid, and dipyridamole is usually advised to prevent stent thrombosis. Monitoring of prothrombin fragments 1 + 2[8] and application of vascular hemostasis devices after coronary stenting[9] are reported as possible means of optimizing heparin therapy during adjustment on coumadin. It is not surprising that entry site–related bleeding complications are frequently encountered in the days after stent implantation. The incidence of puncture site–related complications has been reported to vary between 7.9% of 226 patients in the initial multicenter experience with the Palmaz-Schatz stent[2] and 16% of 220 patients in a large single-center experience.[10] A bleeding complication has serious local sequelae and may force the clinician toward suboptimal heparinization and increased risk of stent occlusion. One possible solution for prevention of severe puncture site–related events may be found in the combination of a smaller puncture opening with selection of another entry site.

Stent implantation through 6F guiding catheters. In recent years development of miniaturized PTCA equipment allowed the use of 7F,[11] 6F,[3,12,13] and even 4F[14] guiding catheters for coronary angioplasty. Transfemoral artery stent implantation through 6F guiding catheters has been reported in three patients by Urban et al.[15] Our results also show that 6F guiding catheters accomodate stent-loaded, low-profile balloon catheters well.

Adequate back-up support allows passage of a metallic stent on an unlubricated balloon catheter across a coronary stenosis. For this reason a guiding

catheter curve that provides optimal support has to be selected. Pressure damping in the coronary ostia by these guiding catheters was not encountered. Accurate positioning of the stent in relation to the stenosis was feasible as a result of adequate opacification of the vessel with contrast medium. Balloon retrieval after stent delivery and balloon exchange for stent oversizing were also easily accomplished. However, a hazardous limitation of this approach should be emphasized. Because prefabricated sheath-protected stent delivery systems cannot be advanced through 6F guiding catheters, friction between the stent and the guiding catheter tip (friction was noticed in two of four patients in whom an Amplatz-shaped catheter was used) or vessel wall may shear the bare stent from the balloon, potentially leading to stent embolization. To minimize this risk, optimal coaxial alignment between the guiding catheter and coronary artery should be obtained before stent implantation is attempted. We crimp the stent on the balloon after it has been inflated several times to increase balloon profile and allow better fixation to carry the stent. Removal of the lubricating coating from the balloon also helps to keep the stent fixed to the balloon. We recommend predilating a tight stenosis because this will fascilitate stent passage. Despite these precautions, displacement of the stent from the balloon catheter occurred in one patient during an attempt to retrieve the stent-loaded balloon within the guiding catheter. Another limitation at present is the inability to use intravascular ultrasound or angioscopy to assess obstructions distal to a stent or suspected suboptimal stent deployment. In these instances large bore catheters are preferred. Because 6F guiding catheters accomodate low-profile ACS Flowtrack 40 M perfusion balloon catheters, prolonged dilatations with preservation of distal flow are no longer precluded after a 6F guiding catheter is selected.[16]

Stent implantation via the radial artery. Dorros et al.[17] described an alternative route for PTCA by performing arteriotomy of the brachial artery. At present extensive experience with percutaneous transbrachial coronary catheterization and angioplasty shows them to be effective and safe alternatives to the Sones technique and the percutaneous technique of the femoral artery.[18-20] Complications after brachial artery puncture are rare, but if present they often require surgical repair. Complications are arteriovenous fistulae, nerve injury, thrombotic artery obstruction, dissection, and false aneurysm.[21]

Campeau[21] reported percutaneous entry of the radial artery for cardiac catheterization in 100 patients with a collateral blood supply to the hand. An arterial sheath with an internal diameter of 5F was used. Only two symptomless vascular complications were observed. Safety of transradial artery coronary catheterization is mainly determined by the favorable anatomic relations of the radial artery to its surrounding structures and the double blood supply to the hand. The sequelae of radial artery obstruction are frequently mild even in patients not selected for good collateral circulation. Slogoff et al.[22] reported a series of 1699 patients who underwent heart surgery with perioperative radial artery cannulation. No ischemic damage to the hand was observed, even in 25% of patients with abnormal Doppler flow patterns, compatible with partial or complete radial artery occlusion. No major veins or nerves are located near the radial artery excluding injury of these structures. Because of the superficial course of the artery, hemostasis can be easily obtained with local compression. Feasibility and safety of transradial artery PTCA was demonstrated by our group in 100 consecutive patients, with a procedural success rate of 98% (92% via the radial artery) and absence of major puncture site–related complications, leading to functional disability of the hand, vascular surgery, or need for blood transfusions.[3]

We attempted a transradial artery stent implantation irrespective of gender, age, body weight, and height of patient. All patients selected for stenting had successful radial artery puncture and cannulation. Our results indicate that transradial artery catheterization with 6F guiding catheters can be performed within acceptable time limits and without major discomfort for the patient. Immediate ambulation of the patient after stenting is associated with increased patient comfort. The sheath was removed immediately after the procedure to reduce the risk of radial artery thrombosis.[23] Even in heparinized patients, hemostasis was obtained at a mean interval of 31 minutes.

No clinical puncture site–related complications were encountered that required blood transfusions or vascular surgery. The absence of postprocedural radial artery occlusion compares favorably with reported incidences of 6% in the series of Campeau,[21] 30% of 333 radial artery cannulations in the series of Davis and Stewart,[24] and 38% described by Bedfort and Wallman.[23] Early sheath removal and combined anticoagulation may have contributed to this favorable outcome.

Potential benefit. By using one dilatation catheter for predilatation, stent delivery, and oversizing and by using a bare stent, considerable reduction in ma-

terial cost can be achieved. We used 1.9 dilatation catheters per procedure including bail-out procedures where multiple balloon catheters were used before stent implantation. Reduction of vascular complications and subsequent treatments also contribute to reduced cost. A potential advantage of the transradial artery approach is early discharge of the patient after stent implantation. The mean duration of hospital stay after stent implantation in this study was 6 days. However, if the elective stent candidate is adjusted on coumadin before hospital admission, there is no other argument for prolonged hospitalization if the stent result is optimal.

Conclusions. When appropriate precautions are taken, transradial artery coronary stent implantation with miniaturized angioplasty equipment is feasible and safe, although the limitations of the "bare-stent technique" remain a concern. A major benefit of this approach is a reduction in clinical puncture site–related complications and patient comfort. To establish the potential superiority of this approach over the transfemoral approach, a larger sample size should be studied, ideally in a prospective randomized fashion.

SUMMARY

The purpose of this study was to evaluate feasibility, safety, and efficacy of implantation of unsheathed Palmaz-Schatz coronary stents via the radial artery. Anticoagulation after coronary stenting has the hazard of vascular complications if large-bore guiding catheters are introduced via the femoral artery. Such complications have serious local sequelae, are associated with suboptimal anticoagulation, and prolong hospitalization. By combining 6F guiding catheters and low-profile dilatation catheters with bare Palmaz-Schatz stents, smaller vessels such as the radial artery can be selected as the entry site. It is postulated that no major puncture site–related complications occur because hemostasis is easily achieved and no veins and nerves are near the radial artery. With double blood supply to the hand, radial artery occlusion is well tolerated. Twenty-five bare Palmaz-Schatz stents were implanted via the radial artery through 6F guiding catheters in 20 consecutive patients for venous bypass graft stenosis (n = 9; 45%), native coronary artery restenosis (n = 7; 35%) and suboptimal transradial artery PTCA (n = 4; 20%). Immediately after stent implantation and assessment of the result by means of computerized quantitative coronary analysis, the arterial sheath was withdrawn followed by intense anticoagulation and free ambulation of the patient. Radial artery function and anatomy were assessed by two-dimensional and Doppler ultrasound examination. Lesions (n = 24) were of type A (n = 13; 54%), B (n = 6; 25%) and C (n = 5; 21%). The reference diameter of the stented segments was 3.2 ± 0.5 mm (2.2 to 4.2 mm). Procedural success via the radial artery was 100%. However, one patient had a non-Q myocardial infarction as a result of occlusion of a diagonal branch after predilatation of a stenosis in the left anterior descending coronary artery. In the same patient, oversizing the distal of three stents resulted in a distal antegrade dissection, for which a fourth stent was successfully implanted. Minimal luminal diameter increased from 0.9 ± 0.4 mm (0 to 1.7 mm) to 3.1 ± 0.4 mm (2.4 to 4.1 mm), and diameter stenosis was reduced from 71% ± 12% (52% to 100%) to 13% ± 10% (0% to 32%). Hemostasis was obtained within 32 ± 11 minutes (20 to 60 minutes) after the procedure. No puncture site–related complications were encountered. One patient had macroscopic hematuria, which subsided spontaneously. No blood transfusions were required. No patient suffered from stent occlusion. In all patients the radial artery was patent at discharge. Coronary stenting via the radial artery is feasible and safe, excludes major entry site–related complications, and facilitates postprocedural patient management.

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CHAPTER 4.6.3

POTENTIAL SOLUTIONS

RADIAL ARTERY AS ENTRY SITE

Transradial artery coronary stent implantation

TRANSRADIAL ARTERY PALMAZ SCHATZ CORONARY STENT IMPLANTATION: RESULTS OF A SINGLE CENTER FEASIBILITY STUDY

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Transradial artery Palmaz Schatz coronary stent implantation: Results of a single center feasibility study.

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ABSTRACT

Objectives. The purpose of this study was to evaluate feasibility and safety of implantation of unsheathed Palmaz Schatz coronary stents via the radial artery.
Backgrounds. Anticoagulation after coronary stenting carries the risk of vascular complications if large bore guiding catheters are introduced via the femoral artery. Such a complication has serious local sequelae and leads to suboptimal anticoagulation and prolonged hospitalization. By combining 6 French (F) guiding catheters and low profile dilatation catheters, mounted with Palmaz Schatz stents, smaller vessels such as the radial artery, can be selected as entry site. It is postulated that major puncture site related complications rarely occur because hemostasis is easily achieved and no veins and nerves are near this artery. With double blood supply to the hand, radial artery occlusion is well tolerated.
Methods. In 100 consecutive patients, stent implantation was attempted for 122 lesions, distributed in 104 vessels. Immediately after stent implantation and final angiography, the introducer sheath was withdrawn, followed by intense anticoagulation and mobilization. The radial artery puncture site was studied by two-dimensional and Doppler ultrasound.
Results. Successful stent implantation via the radial artery was achieved in 96 patients. In 2 patients, arterial puncture failed, followed by successful stenting via another entry site. In 1 patient, stent implantation was achieved with a stent delivery system via the femoral artery, after a failed attempt to cross the lesion with a bare stent via the radial approach, complicated by a groin bleeding requiring transfusions and vascular surgery. One patient was referred for coronary bypass surgery, because the stent could not reach a dissection in a tortuous LAD. Lesions were of type A (n=43 [35%]), B (n=30 [25%]) and C (n=49 [40%]). Reference diameter of the stented segments was 3.3 ± 0.5 mm (1.2 - 5.0 mm). Minimal luminal diameter increased from 1.1 ± 0.4 mm (0 - 2.1 mm) to 3.1 ± 0.5 mm (1.0 - 4.2 mm). Diameter stenosis was reduced from 67 ± 11% (37 - 100%) to 13 ± 10% (0 - 68%). Procedural success and an uncomplicated clinical course was achieved in 93 patients (93%). One patient (1%) had subacute stent thrombosis, followed by successful PTCA and coronary bypass surgery. Another patient died 2 days after stenting for unstable angina and a poor left ventricular function, without signs of stent occlusion. One patient developed a radial artery bleeding, requiring surgical repair. None of the 4 pts with a post procedural radial artery occlusion showed signs of ischemia of the hand. Hospital stay was 5.2 ± 4.1 days. Patients (n=64) using coumadin at admission, were hospitalized for 4.1 ± 4.2 days. Of this population, 22 patients (34%) were discharged within 24 hours after stenting.
Conclusion. Transradial artery Palmaz Schatz coronary stenting is feasible and safe. Under intense anticoagulation early major entry site related complications are rarely encountered.

INTRODUCTION

Implantation of metallic coronary stents via the femoral artery, under complex anticoagulation regimens (1), carries a substantial risk for bleeding complications, especially if large bore guiding catheters are used (2,3,4,5). A possible solution to prevent severe puncture site related events may be found in the combination of a smaller puncture opening with selection of an other entry site. With the introduction of 6 French guiding catheters that allow passage of low profile balloon catheters, percutaneous balloon angioplasty via the radial artery became possible, as demonstrated by our group in 100 consecutive patients (6).

This report describes the technique, procedural results and clinical course in 100 consecutive patients who underwent Palmaz Schatz coronary stent implantation via the radial artery.

METHODS

Patient selection

From March 1993 to May 1994, 100 patients were selected for coronary stent implantation via the radial artery. Excluded for this approach were patients with absence of collaterals from the ulnar artery, as assessed by the Allen- test. The Allen- test was considered normal when after compression of both ulnar and radial arteries, a return of the normal colour of the hand occurred within 10 seconds after release of occlusion of the ulnar artery. Included were also patients with a suboptimal result after transradial artery PTCA.

Medical treatment

Medical treatment has been described previously by our group (7,8). In the course of this study, however, more elective patients were pretreated with coumadin, in order to reduce the hospitalization time. The INR was assessed just prior to the procedure. At an INR > 2.7, the patient received 10.000 IU heparin after sheath insertion, together with Dextran 40 (a total of 1 liter) and Acetylsalicylic acid 500 mg intravenously. No heparin was given after the procedure. At an INR < 2.7, heparin was titrated to an APTT of 80 seconds after a 3.000 IU bolus, three hours after hemostasis was achieved. Heparin was gradually stopped at an adequate INR > 2.7.

Transradial PTCA technique

The technique for radial artery catheterization, coronary cannulation, angioplasty, stent implantation and quantitative coronary analysis, has been described previously (7,8).
In brief; The right arm was abducted and the wrist hyperextended. After local anaesthesia, the radial artery was punctured with an Arrow®, 22 gauge radial artery catheterization set or with a Kimmal® needle. After appearance of pulsatile flow from the needle an 0.025 inch, 260 cm long, J shaped guidewire (Schneider®) was introduced through this system, followed by insertion of a 6 French arterial introducer. During ongoing experience, we preferrably used 23 cm, instead of 10 cm long Terumo® 6F introducer sheaths, to prevent radial artery spasm and to facilitate guiding catheter manipulations.
Meticulous care was directed towards optimal selection of the guiding catheter, with respect to backup support and coaxial alignment. The Cordis® Petite™ 6F guiding catheter was preferrably selected because of its large inner diameter (0.062 inch). For left coronary artery procedures, the Scimed® Triguide™ 6F Voda- curve was selected because of optimal support and alignment, despite a smaller inner diameter (0.060 inch). Later in the study, this curve also became available from Cordis® (Extra Backup™). We selected Scimed® Express™ balloon catheters for predilatation and stent delivery, because of it's low profile, ease of advancement over the guidewire and through the guiding catheter and because of the proper fixation of the stent, once crimped on the balloon.
One or more 7 mm, 10 mm or 15 mm Palmaz Schatz coronary stents (Johnson and Johnson Interventional Systems, Warren, NJ) were used. After delivery, the stent diameter was optimized by successive dilatations with higher inflation pressures or with larger balloon catheters of intermediate compliance (Schneider® Magical Speedy™).

Prevention of stent embolization

After a failed attempt to advance the stent into the coronary artery or across the target lesion, two strategies were applied to prevent stent loss or embolization. If intracoronary withdrawal of the stent loaded balloon, back into the guiding catheter, was considered to result in dislod-

gement of the stent, the stent was deployed proximal from the target lesion, if that coronary segment was suitable for stent implantation. In other instances, the stent loaded balloon was retrieved to a position just outside the guiding catheter. Preferrably over the intracoronary guide wire, the entire system was withdrawn into the brachial or radial artery, without a change of the mutual position of guiding catheter and balloon catheter. Only in the brachial or radial artery, an attempt was made to withdraw the balloon catheter into the guiding catheter. If the stent became detached from the balloon, the balloon and guiding catheter were removed and a looped snare, made of an intracoronary guidewire, was advanced through the sheath and over the guide wire towards the lost stent. After capture of the stent, the loop was closed allowing stent retrieval into introducer sheath.

Introducer sheath removal and hemostasis
The arterial sheath was removed, immediately after withdrawal of the guiding catheter, followed by application of an occlusive tourniquet at the radial puncture site for a minimum of 30 minutes. Pressure was gradually released until hemostasis was obtained. A pressure dressing over the punctured artery was applied for 6 hours. Patients were encouraged to mobilize, and advised to restrict movements of the wrist joint.

Predischarge examinations
The radial artery was controlled for the presence of pulsations, the Allen test and the reversed Allen test. Claudication of the hand was tested by opening and closing the hand 50 times. A two-dimensional and Doppler ultrasound study was performed prior to discharge.

Statistical Methods
All values are expressed as mean ± standard deviation.

RESULTS

Study population
Between March 1993 and May 1994, in 100 consecutive patients transradial artery implantation of a Palmaz Schatz stent was attempted for native coronary artery restenosis after previous angioplasty (n=33, 33%), saphenous vein coronary bypass stenosis (n=31, 31%), for de novo native coronary artery lesions (n=27, 27%) and for a suboptimal PTCA result (n=9, 9%). For 122 lesions, 146 stents were implanted in 104 vessels. During the course of this study, stent implantation via the femoral or brachial artery was only attempted in those patients, participating in other stent- studies or undergoing emergency stenting after failed PTCA via the femoral or brachial route. Table I displays baseline clinical characteristics.

Angiographical data
Vessel distribution and lesion morphology are displayed in Table II.
Quantitative coronary angiographical data are listed in Table III.

Procedure
Overall, a successful stent implantation via the radial artery was achieved in 96 patients (96%). A successful transradial stent implantation, together with an uncomplicated clinical course (no death, coronary artery bypass surgery, Q- wave myocardial infarction, stent occlusion, repeat PTCA, vascular surgery or blood transfusions) was achieved in 93 patients (93%).

Table I. Baseline characteristics

		N	
No. patients		100	
Male gender		82	
Age (years)		64 ± 11	(range 35 - 89)
Height (cm)		174 ± 8	(range 149 - 193)
Weight (kg)		81 ± 10	(range 58 - 112)
Oral anticoagulation			
Acetyl salicylic acid		75	
Dipyridamol		16	
Coumadin		64	
Exertional angina;	CCS I	1	
	CCS II	11	
	CCS III	45	
	CCS IV	38	
Non exertional angina		43	
Mixed angina		38	
Prior myocardial infarction		35	
Prior bypass surgery		49	
Hypertension		24	
Diabetes mellitus		27	
Cholesterol ≥ 6.5 mmol/l		30	
Smoking history		48	
Family history		16	

Table II. Angiographical data.

	N	(%)
Stented vessels (n=104)		
LM	2	(2%)
LAD	34	(34%)
LCX	14	(13%)
RCA	23	(24%)
VBG	31	(27%)
Lesion morphology (n=122) *		
Type A	43	(35%)
Type B	30	(25%)
Type C	49	(40%)

LAD Left anterior descending coronary artery
LCX Left circumflex coronary artery
LM Left mainstem
RCA Right coronary artery
VBG Venous bypass graft
* Reference 28.

Table III. Quantitative coronary angiography

	Baseline		Post stenting	
	Mean ± SD	Range	Mean ± SD	Range
Reference diameter (mm)	3.3 ± 0.5	1.2* - 5.0	3.5 ± 0.5	2.2 - 5.1
Minimal lumen diameter (mm)	1.1 ± 0.4	0 - 2.1	3.1 ± 0.5	1.0 - 4.2
Diameter stenosis (%)	67 ± 11	37 - 100	13 ± 10	0 - 68

* Inadvertent deployment of a stent, distal from an LAD- dissection after PTCA

Radial artery cannulation

The radial artery was successfully punctured and cannulated in 98 patients (98%).
In one 89 year old patient the radial artery, weak at palpation, could not be punctured, followed by successful transfemoral stent implantation via 6F guiding catheters of the mainstem (LM) of the left coronary artery (LCA) and of the ostium of the right coronary artery (RCA). The other patient underwent stenting via the brachial artery of a venous bypass graft (VBG) and of a restenosis in the left circumflex coronary artery (LCX), immediately following a failed attempt to puncture the radial artery.

Guiding catheter selection and performance

For 104 vessels, 170 guiding catheters were used (1.7 catheter per procedure). Venous bypass grafts and the RCA were usually cannulated with El Gamal or Multipurpose- type guiding catheters (81% and 65%, respectively). The most frequently used catheter for the LCA had a Voda-left curve (52%). An overview of guiding catheters used for stent implantation is given in Table IV. For these catheters, contrast opacification and pressure monitoring were rated good in all instances. Good back-up support was obtained during stent implantation in 88 cannulated vessels (85%). Backup support was moderate to poor in 16 instances (15% of cannulated vessels), but with these catheters, the procedure could be successfully completed in 13 patients. In 1 patient the procedure had to be continued via the femoral artery with an 8F guiding catheter to allow passage of a sheath protected stent delivery system across a proximal LAD dissection. In another patient, a stent could not cross a proximal insignificant stenosis in a venous bypass graft, due to poor coaxial alignment. With another guiding catheter, the procedure could successfully be continued. In a third patient the guiding catheter did not provide enough support to advance a 7 mm stent at the target lesion in the LAD. In an attempt to withdraw the stent within the guiding catheter, displacement of the stent towards the distal end of the balloon was noticed. This stent was incompletely deployed in the LAD, proximal from the target lesion, and could not be crossed by the same balloon catheter. With a 2.0 mm balloon catheter, this stent could be expanded, followed by optimal deployment with a 3.5 mm balloon catheter. With the use of another guiding catheter, the target lesions were successfully stented.

Balloon catheter selection and performance

A total of 156 balloon catheters were used (1.6 balloon per patient and 1.0 balloon per stent).

Predilatation

During elective procedures the lesions were predilated, except in 2 patients. Predilatation was performed at low inflation pressures with adequately sized balloons, also suitable for stent delivery and secondary dilatations if necessary. After selection of the optimal guiding catheter, the balloons could successfully be positioned and retrieved across the stenosis. However, in one patient the balloon could not cross a tight stenosis in the LAD. After several passes

with a rotablator (burr-size 1.25 mm) the procedure could be continued successfully.
Following predilatation of a stenosis in the LAD, a major diagonal branch occluded in one patient. This branch remained occluded during the procedure and after stent implantation and resulted in a non-Q myocardial infarction (CPK-MB 64 mmol/l). In one patient selected for elective stenting of a restenosis in the RCA, predilatation resulted in a local dissection and subtotal occlusion, well managed after implantation of one stent. In another patient, predilatation of a restenosis in the LAD, was complicated by a distally progressing dissection, successfully stabilized after implantation of 4 stents.
Predilatation did not result in complications in the other patients, although one patient with a membrane-like stenosis in the LAD did not show any improvement after predilatation with an adequately sized balloon.

Stent delivery
Opacification of the vessel containing the deflated, stent loaded balloon, easily allowed adequate positioning of the stent in relation to the culprit lesion.
For 122 lesions, 146 stents (15 mm: n=121; 7 mm: n=20; 10 mm: n= 5) were successfully implanted (1.5 stent per patient {range 1-5}). Multiple stents were implanted for multiple lesions (15 patients) or to cover residual obstructions or dissections near the stent (10 patients). In two of these 10 patients a stent was inadvertently deployed too distally. In one patient a second stent was deployed at the proper site in patient. In the other patient a third stent had to be implanted distal from the misplaced stent, in order to correct an acute transition in diameter between the stent and the small distal segment (RD 1.2 mm). Outcome of these patients was uneventful. In one patient it was not possible to stent a dissection half-way in a tortuous LAD, despite adequate backup support from the guiding catheter, because the stent loaded balloon could not reach the lesion. This stent was deployed proximally from the target lesion in order to prevent stent loss or embolization during attempts to retrieve the balloon. This patient was referred for emergent coronary bypass surgery in a stable condition. The post-operative course was complicated by a non-Q- wave myocardial infarction (CKMB 79 IU/l).
In one patient the stent, mounted on a 3.5 mm balloon catheter used for predilatation, could not enter a venous bypass graft. A successful attempt was performed with a 3.0 balloon catheter as stent carrier. In another patient, a stent, crimped on a 3.5 mm balloon catheter, could not cross a proximal stent, implanted in the RCA. With a new balloon catheter the procedure could be completed. In these patients the dispatched stents were retrieved successfully from the radial artery. No stents were lost.

Secondary stent dilatations
In 29 patients the result was considered to be optimal after stent delivery. In the remaining 70 patients the stents were dilated at higher inflation pressures with the same balloon catheter or with semi-compliant balloon catheters, to optimize stent deployment.
In one patient, undergoing stent implantation for an obstructive dissection of the circumflex coronary artery after PTCA, three balloon catheters could not cross a well deployed stent in the LCX, in order to improve a residual dissection distal from the stent. With aggressive anticoagulation, this patient had an uncomplicated clinical course.
High pressure dilatation of the stented segment with a larger balloon catheter was associated with the appearance of a dissection near the stent in 3 patients, requiring additional stent implantation.

Angiographical results
All stents were angiographically well deployed. Quantitative analysis data are summarized in Table 3. A small filling defect within the stent was visible in 5 stents (3,4%).
At 11 stented sites (7,4%) some contrast medium remained visible parallel to the vessel, outs-

ide the stent.

Hemostasis

The arterial sheath was removed immediately after the last control angiogram, except in the patient who had bypass surgery after a failed attempt to implant a stent in a dissected LAD-segment after PTCA. The tourniquet was replaced by a pressure dressing after 33 ± 17 minutes (range 0 - 120). In two patients some collagen (Vasoseal®) was successfully applied subcutaneously near the puncture opening to stop prolonged bleeding.

Clinical course

Cardiac complications

One patient developed subacute stent thrombosis, 5 days after a double stent implantation, following PTCA of the LAD, which resulted in a long dissection.
Allthough a small residual dissection remained visible in between both stents, this result was considered acceptable. The patient was adequately adjusted on coumadin at the time of stent occlusion. After successful recanalization by immediate PTCA, this patient was referred for emergent coronary bypass surgery. The patient developed a non-Q myocardial infarction.
One 73 year old male patient died in cardiogenic shock, the day after stent implantion proximal in a subtotally occluded LCX, for unstable angina pectoris. This patient had a poor left ventricular function caused by an old anterior infarction. An optimal result was obtained during an uncomplicated stent procedure. At autopsy, the stent was patent without signs of thrombus. The left ventricle showed extensive fibrosis by old myocardial infarction, with evidence of more recent necrosis. Another patient had temporary anginal complaints without EKG- changes, 2 hours after successful stent implantation of a lesion in the LCX. Because of a rise in the cardiac enzymes (CKMB 42 IU/l), a control angiogram was made the following day. Normal flow was visible, with a dissection in the LCX, extending from the distal part of the stent into a marginal branch. No other stent related cardiac complications were registred.

Bleeding complications

One patient developed a subcutaneous bleeding of the hand and forearm 2 hours after the procedure, requiring acute vascular repair and decompression of the hematoma. During hospitalization, no other vascular surgery or blood transfusions in relation to the radial approach were indicated. Four patients had transient hematuria, without need for additional treatment.
Another patient had temporary oculomotoric dysfunction due to a transient ischemic attack. A CT- scan of the brain was normal.

Hospitalization

Hospitalization was prolonged to 29 days in one patient requiring intravenous antibiotic treatment for fever caused by a Staphylococcus aureus bacteremia, related to a contaminated intravenous cannula. Patients were discharged 5.2 ± 4.1 days (range 0-29) after stent implantation. From the 64 patients, using coumadin on admission, 22 patients (34%) with an INR > 2.7, could be discharged the day following stent implantation. Mean duration of hospital stay of all patients using coumadin was 4.1 ± 4.2 days (0-29).

Doppler and physical radial artery studies

In 96 patients normal radial artery pulsations were palpable at discharge. Doppler ultrasound examination proved the presence of flow at the puncture site in these patients. None of the 4 patients with absent pulsations had symptoms or complaints of ischemia of the forearm and hand. During follow-up, a pseudoaneurysm was encountered in 3 patients. In 1 of these patients the pseudoaneurysm disappeared spontaneously. Because of associated discomfort, the 2 other patients underwent elective local surgical repair one and 3 months following stent implantation and after discontinuation of coumadin.

Table IV. Guiding catheters used for stent implantation (n=104)

	RCA	LM	LAD	LCX	VBG	Total
El Gamal	8	0	5	0	21	34
Multipurpose	7	0	0	0	4	11
Voda Left	0	2	14	10	2	28
Judkins Left	0	0	13	2	0	15
Judkins Right	5	0	0	0	0	5
Amplatz Left	0	0	2	2	3	7
Amplatz Right	3	0	0	0	1	4
Total	23	2	34	14	31	104

LAD Left anterior descending coronary artery
LCX Left circumflex coronary artery
LM Mainstem left coronary artery
RCA Right coronary artery
VBG Venous bypass graft

DISCUSSION

Implantation of coronary stents for coronary artery disease aims at improvement and optimalization of coronary geometry in order to reduce the incidence of restenosis of de novo lesions in native coronary arteries (2,3), in venous bypass grafts (5), refractory restenosis (9), and to treat dissections and suboptimal results after balloon angioplasty (10,11,12). The problems encountered after implantation of metallic stents are two-fold; risk of stent thrombosis requiring aggressive anticoagulation and as a consequence the risk of access site related bleeding complications. Although new insights may have resulted in a lower incidence of stent thrombosis, bleeding complications still remains a matter of concern, not only because of associated morbidity and mortality, but also because of patient comfort, prolonged hospitalization and cost effectiveness.
Several strategies have been developed in order to reduce the incidence of bleeding complications. A number of hemostasis devices have been recommended in order to obtain fast, stable and save hemostasis after coronary catheterization or angioplasty, such as collagen plugs (13,14), the Kensey device (15) and mechanical compression devices (16). The role of these devices still remains a matter of debate, since safety and efficacy are not convincingly reported and since its application increases the costs of the technique.
Reduction of the anticoagulation regimen may be associated with less bleeding complication. This may be only be possible after introduction of heparin coated stents (17) or after optimal deployment of the stent as assessed by intravascular ultrasound (18,19,20,21).
At this moment there are promising reports on the treatment with only platelet aggregation inhibitors together with subcutaneous heparin (22,23) after an optimal stent result.
Another modality is the use of less traumatic, 6F guiding catheters for transfemoral stent implantation. Although the sheath protected stent technique has to be abandoned for this approach, Palmaz Schatz stents can be implanted successfully (24).

Miniaturization of angioplasty equipment made selection of smaller arteries as entry sites such as the radial artery, possible. Campeau reported on transradial coronary angiography with 5F catheters (25). Major advantages of this approach are the superficial course of the radial artery, the absence of major veins and nerves close to the radial artery and the presence of collaterals between the radial and ulnar arteries. As a consequence, hemostasis can be obtained easily and safely, nerve damage and arteriovenous fistula occur rarely and ischemia of the hand is prevented, in case the radial artery becomes occluded. In a previous study from our institution, of 100 patients who had PTCA via the radial artery, a procedural success was obtained in 92% of patients and no major vascular complications, requiring vascular surgery or blood transfusions were encountered (6).
Bailout techniques such as the use of perfusion balloons (26,27) and stents (27) can successfully be applied after PTCA by the 6 French transradial approach, increasing safety of this technique.
In the current study, success rate of stent implantation via the radial artery was 96%, which compares favorably with results of stenting via 8F guiding catheters. Procedural success in the Benestent study was 93.2% (stent implantation failed in 17 of 251 attempts; 6.8%) (2). Procedural success in the STRESS- study was 92.3% (3). The high successrate and a low incidence of stent occlusion (1%) contributed to the favorable clinical outcome in 93% of the current study population, despite the fact that patients were included with more complex coronary anatomy such as ostial lesions and type C lesions (28), saphenous vein graft disease, restenosis and suboptimal PTCA- results.
The incidence of puncture site related complications, has been reported to vary between 7.9% of 226 patients in the initial multicenter experience with the Palmaz Schatz stent (1) and 16% of 220 patients in large single center experience (4). In the study of Piana et al, reporting on Palmaz Schatz stenting in vein grafts, vascular repair was necessary in 8.5% and transfusions in an additional 14% (5). Bleeding complications requiring vascular surgery or transfusions was reported in 13.7% of patients after stent implantation in the Benestent study (2) and in 6.8% in the STRESS- study (3).
The major advantage of the transradial approach for coronary stenting is illustrated by the low incidence of radial artery related early bleeding complications (1%). The promise of this technique in prevention of local bleeding complications is even more pronounced, since the sheath was withdrawn immediately after the procedure in fully heparinized patients, most of them under a partial or complete preprocedural level of oral anticoagulation. The indidence of chronic radial artery occlusion was 3 to 5% in our PTCA experience (6) and 4% in our stent experience. This is in contrast with high radial artery occlusion rates after perioperative intraarterial monitoring; 30% and 38% as reported by Davis et al. (29) and by Bedfort et al. (30) respectively. Ischemic symptoms after radial artery occlusion were absent in our study, because only patients with collateral blood supply to the hand were selected. In the series of Bedfort et al. 105 radial artery cannulations were prospectively studied in 100 patients. Radial artery thrombosis was found in 40 patients (38%) without major ischemic complications. Mandel e.a. reviewed 1.000 radial artery cannulations (31). The cannulas were removed after 5 hours to 5 days. Distal ischemia, requiring embolectomy or vascular reconstruction was necessary in 2 patients (0.2%). Slogoff et al. analysed 1.699 patients who had prolonged radial artery cannulation for monitoring purposes after cardiac surgery (32). Although 25% of patients had deminished or absent flow during Doppler examination, no ischemic damage or disability of the hand occurred in any patient. Based on our experience and on these reports, we consider radial artery cannulation as a low risk entry site, even if post procedural radial artery patency is absent. Immediate withdrawal of the sheath under anticoagulation may have contributed to both this low occlusion rate, as well as the 3% incidence of late pseudoaneurysm formation.
Early mobilization of the patient, a low incidence of bleeding complications, and preprocedural adjustment on oral anticoagulation, resulted in a hospital stay of 5.2 ± 4.1 days for the total

population and of 4.1 ± 4.2 days for patients using coumadin before admission. From these 64 patients receiving coumadin before the procedure, only 22 patients (34%) had an INR > 2.7 and these patients could be discharged the day following stent implantation. This shorter hospitalization time may reduce cost of this technique, since Cohen et al. found hospital charges after stenting 35-45% higher than for other interventions, due to a longer hospital stay and more expensive utilization of resources (33). Costs may further be reduced by a reduced use of angioplasty material (1 balloon per stent), despite the higher consumption of guiding catheters, and by less costs for diagnosis and therapy for bleeding complications.
Certain limitations of this approach should be mentioned. Although most patients have a collateral connection with the ulnar artery, some patients have to be excluded if the radial artery is the only artery supplying the hand. In that case a transradial procedure via the left arm can be considered if the Allen- test is normal at that site. Protected angioplasty by intraaortic balloon pumping also is evidently incompatible with the transradial approach. Should this support be necessary during a transradial PTCA, the balloon has to be inserted via the femoral artery. For this reason and for a potential failed transradial attempt, we routinely prepare one of the groins for a transfemoral continuation of the procedure.
Stent implantation through 6F guiding catheters, requires optimal back-up and coaxial alignment in order to facilitate advancement of the stent loaded balloon and to prevent stent loss and embolization. Since most guiding catheters are produced for application via the femoral artery, optimal cannulation via the right radial artery may be difficult to achieve, resulting in a high number of guiding catheters used. Frequent guiding catheter exchanges, may induce spasm of the radial artery. Therefore, we recommend the use of long (23 cm) sheaths and of exchange wires. Although no serious sequelae of stent embolization has been described, the potential for life-threatening complication remains, such as stent embolization to the cerebrovascular circulation. After a failed attempt to cross a stenosis with a stent, retrieval of the stent into the guiding catheter should not be attempted in the ascending aorta, but in the brachial or radial artery. If the stent detaches from the balloon, the stent can be captured by the technique initially described by Pan et al.(34) and modified for the radial artery approach, as described in the "Methods"- section.
Despite these limitations we consider the transradial stent implantation technique as a safe approach with high success rates and a low incidence of bleeding complications, even under aggressive anticoagulation. It is associated with increased patient comfort and this approach has the potential for short hospitalization times and for significant cost reduction.

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CHAPTER 4.6.4

POTENTIAL SOLUTIONS

RADIAL ARTERY AS ENTRY SITE

Transradial artery coronary stent implantation

PERCUTANEOUS TRANSRADIAL CORONARY PALMAZ SCHATZ STENT IMPLANTATION, GUIDED BY INTRAVASCULAR ULTRASOUND

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Percutaneous Transradial Coronary Palmaz-Schatz Stent Implantation, Guided by Intravascular Ultrasound

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Intravascular ultrasound (IVUS) allows accurate assessment of stent deployment, its use being confined to the use of 8 French (F) guiding catheters. We evaluated the feasibility of combining transradial artery Palmaz-Schatz stent implantation through 6F guiding catheters with IVUS for assessment of stent diameter after delivery at moderate inflation pressures (10–12 atmospheres [atm]) with compliant balloons and after high pressure dilatations with balloons of intermediate compliance. In 8 consecutive patients, 12 stents were delivered with Scimed® Express™ balloon catheters at 10–12 atm followed by IVUS (EndoSonics® CathScanner; Visions® FX 3.5F 20 MHz transducer). An ultrasound study was repeated after high pressure dilatations (16–20 atm) with Schneider® Magical Speedy™ balloon catheters. The balloon diameters were derived from manufacturer provided specifications. In all patients the transducer could easily be advanced through the guiding catheters. Reference diameter of the stented segment was 3.7 ± 0.5 mm (2.7–4.5) and the diameter of Scimed® Express™ balloons during inflation was 4.0 ± 0.3 mm (3.6–4.7). Stent diameter was 3.0 ± 0.1 mm (2.8–3.2) ($P < 0.001$ compared to the reference and the balloon diameter). The diameter of the Schneider® Magical Speedy™ balloons at secondary dilatations with 16 ± 3 atm (14–20) was 4.1 ± 0.4 mm (3.3–4.5) ($P = 0.50$ compared to the initial balloon diameter). Final stent diameter was 3.3 ± 0.4 mm (2.9–4.1) ($P = 0.02$ compared to the initial stent diameter). All stents were symmetrically deployed and well apposed. No damage to vessel or stents was detected after passage of the transducer. Thus ultrasound guided stenting via 6F guiding catheters is feasible, and high pressure dilatations with balloons of intermediate compliance results in better stent expansion than after 10–12 atm inflations with compliant balloon catheters.

Key words: transradial angioplasty, stents, intravascular ultrasound

INTRODUCTION

Intravascular ultrasound (IVUS) plays an important role in optimizing coronary stent techniques. Compared to coronary angiography, IVUS provides superior assessment of stent deployment and geometry [1–6]. The application of IVUS has been limited to the use of 8 French (F) or larger guiding catheters. However, 6F guiding catheters are of value in reducing the incidence of bleeding complications after coronary stenting by creation of smaller puncture holes [7] or by selection of a safer entry site, such as the radial artery [8,9]. This feasibility study was performed to evaluate the possibility of combining transradial stent implantation through 6F guiding catheters and IVUS with a low profile ultrasound transducer.

For stent delivery via 6F guiding catheters, we use the compliant Scimed® Express™ balloon catheter. During ongoing experience we noticed that this stent loaded balloon can be maximally inflated to 10–12 atmospheres (atm), before the balloon ruptures. Therefore, we were interested in the stent diameter and apposition after deployment at these inflation pressures with compliant adequately sized balloons. Additionally, we looked for a possible improvement after secondary high pressure dilatations (14–20 atm) with stronger balloon catheters of intermediate compliance.

METHODS

Patient Selection

In an ongoing study, patients are selected for elective coronary stent implantation via the right or left radial artery, irrespective of patient's sex, weight, and size or

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clinical status. An abnormal Allen-test was considered to be a contraindication. The Allen-test is considered normal when after compression of both ulnar and radial arteries, a return of the normal colour of the hand occurred within 10 sec after release of the ulnar artery.

Medical Treatment

Patients were treated with Dextran 40, the first 500 ml at a rate of 100 ml/hr, the second 500 ml at a rate of 50 ml/hr. The infusion was started 2 hr before elective stent implantation or from the moment the decision was made to implant a stent in acute situations. At the day of stent implantation, dipirydamole 225 mg/day and acetosalicylic acid 300 mg/day was started. After sheath insertion, 10.000 IU heparin was administered intra-arterially, followed by 5.000 IU for each hour the procedure lasts. Three hours after hemostasis is achieved, 3.000 IU heparin was administered intravenously. Heparin was titrated to Activated Partial Thromboplastin Times (APTTs) of 80–100 sec until stable adjustment on oral anticoagulant drug therapy (3 consecutive therapeutic Thrombotests). Coumadin was given for 3 months and acetosalicylic acid and dipyridamole were given for 6 months. In order to prevent radial and coronary artery spasm, 10 mg nifedipine was administered sublingually, prior to radial artery puncture.

Quantitative Coronary Analysis

The X-ray imaging equipment used was the Philips Poly Diagnost C2, equipped with a Digital Cardiac Imaging system (DCI) (Philips Medical Systems, Eindhoven, The Netherlands). Quantitative analysis of coronary segments was performed with this system before angioplasty and after the final ultrasound examination following stent implantation or after the last balloon inflation within the coronary stent.

Transradial Artery Stent Implantation

The technique of transradial artery stent implantation and the medical treatment has been previously described in detail by our group [8]. For the purpose of this study, Cordis® Petite™ 6F guiding catheters were used (inner diameter 0.062 inch, shaft length 100 cm). In all patients the lesions were predilated in order to reduce friction between the stent and the lesion, followed by stent implantation and secondary dilatations.

Palmaz-Schatz stents (Johnson and Johnson Interventional Systems, Warren, NJ) were manually crimped on the balloon catheter. The stents were delivered with Scimed® Express™ compliant rapid exchange balloon catheters. Balloons were selected with a manufacturer specified diameter (at 10–12 atm) at least corresponding to the angiographically assessed reference diameter of the target segment. After delivery, the stent diameter was optimized by secondary dilatations at higher inflation pressures with balloon catheters of intermediate compliance (Schneider® Magical Speedy™).

Intravascular Ultrasound

For this study the EndoSonics CathScanner™ Intracoronary Ultrasonic Imaging System was used, combined with the Visions® FX™ 3,5F, 20 MHz monorail ultrasound transducer, containing 64 Piezoelectric ultrasonic elements, circumferentially mounted in the proximal neck of the catheter. The transducer was positioned under fluoroscopy during injections of contrast medium. Ultrasound studies were performed after stent implantation and after successive post stent dilatations to assess any difference in stent diameters. No ultrasound studies were performed before the initial dilatation, because of anticipated catheter occlusion of the lumen. Reference and stent diameters were determined on-line from real time images, selected in end-diastole. The calipers were diametrically placed at two opposite leading edges of the vessel wall or at the inner surface of the stent filaments. Luminal diameters were recorded as minimal and maximal values. Consensus reading on reference and stent diameters was performed by at least 2 investigators. The last passage of the ultrasonic catheter was followed by angiographic control of the vessel, to detect possible catheter induced damage.

Definitions

The stent was considered to be symmetrically deployed at a ratio of minimal and maximal stent diameters ≥ 0.9. After secondary dilatations a completely deployed stent was defined at a stent diameter >90% of reference diameter or >90% of the final balloon diameter. The stent was considered to be well apposed if no free space between the stent filaments and the vessel wall was detectable.

Statistical Methods

All values are expressed as mean ± standard deviation. Reference and stent diameters were calculated from the mean of minimal and maximal diameters. Differences in diameters were calculated with the t-test. A P value < 0.05 was considered to be statistically significant.

RESULTS

Between October and November 1993 12 stents were implanted in 8 consecutive male patients (61 ± 13 years) who underwent transradial artery ultrasound guided coronary stent implantation for venous bypass graft stenosis (n = 3), native vessel restenosis (n = 3), and native vessel de novo lesions (n = 2). Angiographical and

TABLE I. Angiographical Data*

	N	(%)
No. stents placed (n = 12)		
LAD	1	(8)
RCA	2	(17)
LCX	2	(17)
VBG	7	(58)
TIMI-grade (8 vessels)		
2	1	(13)
3	7	(87)
Type (12 lesions)		
A	6	(50)
B	3	(25)
C	3	(25)

*LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction; VBG, venous bypass graft.

TABLE II. Quantitative Coronary Angiography

	Baseline		Poststenting	
	Mean ± SD	Range	Mean ± SD	Range
Reference diameter (mm)	3.2 ± 0.6	2.4–4.5	3.5 ± 0.8	2.4–4.6
Minimal lumen diameter (mm)	1.1 ± 0.2	0.8–1.5	3.2 ± 0.4	2.7–4.2
Diameter stenosis (%)	60 ± 9	39–71	12 ± 9	0–26

quantitative coronary analysis data are given in Tables I and II, respectively.

Procedure

Radial artery cannulation, coronary angioplasty, stent positioning, and stent delivery were successful in all patients. In all patients, the ultrasound transducer could easily be advanced through the guiding catheter. No problems were encountered during advancement of the transducer towards the stented segment. The position of the transducer-marker in relation to the region of interest was well visualized by contrast agent injections. Marked pressure damping and flow impairment were not encountered. Angiography following ultrasound examinations revealed no signs of transducer caused damage to the stents or vessel wall.

Quantitative Ultrasound Assessments

The manufacturer specified diameters of the Scimed® balloon catheters at 12 atm exceeded reference diameters during 10 of 11 stent implantations. In 1 patient the balloon ruptured during a 10-sec inflation up to 10 atm, resulting in an undersized balloon during stent delivery. Reference diameter of the stented segments was 3.7 ± 0.5 mm (2.7–4.5 mm) and the balloon diameter was 4.0 ± 0.3 mm (3.6–4.7) ($P = 0.09$). Stent diameter however was 3.0 ± 0.1 mm (2.8–3.2) ($P < 0.001$ compared to the reference diameter and balloon diameter). The diameter of balloons used for secondary stent dilatations at 16 ± 3 atmospheres (14–20) was 4.1 ± 0.4 mm (3.3–4.5) ($P = 0.50$ when compared to stent delivery balloon diameter). Although this difference is not significant, stent diameter increased significantly to 3.3 ± 0.4 mm (2.9–4.1) ($P = 0.02$ when compared to initial stent diameter). All stents were symmetrically deployed and well apposed against the vessel wall, although the final stent diameter was smaller than the reference diameter ($P = 0.04$).

DISCUSSION

The transradial artery approach for coronary stenting through 6F guiding catheters is an attractive technique since it is associated with high procedural success rates, a very low incidence of access-site related bleeding complications, and increased patient comfort, as patients are not restricted to prolonged immobilization [8,9]. Most ultrasound transducers are not compatible with 6F guiding catheters and no studies have been reported of the use of IVUS combined with miniaturized angioplasty equipment. In the present study we could demonstrate the feasibility of ultrasound guided stent implantation through 6F guiding catheters, using the EndoSonics CathScanner™ Intracoronary Ultrasonic Imaging System combined with the Visions® FX™ 3,5F, 20 MHz monorail ultrasound transducer. Transducer manipulations, contrast agent delivery, and pressure monitoring were not compromised by guiding catheters with an inner diameter of 0.062 inches.

The low profile of the stent loaded Scimed® Express™ balloon catheter, makes this combination suitable for passage through 6F guiding catheters. However, this stent loaded compliant balloon, does not resist inflation pressures over 10–12 atm. We previously demonstrated that low pressure inflations of compliant stent delivery balloons, results in improperly deployed stents [10]. Therefore, we performed secondary high pressure inflations with a less compliant balloon in order to improve stent geometry. It was a surprising finding that the stent diameter improved after secondary dilatations despite the fact that manufacturer specified balloon diameters did not differ significantly from the initial stent delivering compliant balloon. Therefore, the ideal balloon catheter to predilate the lesion and to deliver and to deploy stents should have a low profile, be of intermediate compliance, since some inflation pressure dependent increase in diameter is useful in order to oversize the stent, and should resist high inflation pressures. Such a balloon

makes a single-balloon stent procedure possible and will further reduce costs of coronary stenting.

Except for the small number of stents studied, another limitation of this study is the comparison between ultrasonically assessed reference and stent diameters on the one hand and manufacturer specified balloon diameters on the other hand, since manufacturer specified balloon diameters are determined under in vitro conditions. Under in vivo circumstances, where vessel wall and obstructing plaque, as well as the stent itself, may influence balloon expansion under given inflation pressures, real balloon diameters probably are significantly different from the specified diameters.

However, these limitations do not alter the practical consequences of the findings of this study: ultrasound guided stent implantation via 6F guiding catheters is feasible, and high pressure dilatations with balloons of intermediate compliance result in better stent expansion than after inflations to burst-pressure with compliant balloon catheters.

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CHAPTER 4.6.5

POTENTIAL SOLUTIONS

RADIAL ARTERY AS ENTRY SITE

Transradial artery coronary stent implantation

COMPARISON OF COSTS BETWEEN TWO MODES OF IMPLANTATION OF PALMAZ SCHATZ CORONARY STENTS: THE TRANSRADIAL BARE STENT TECHNIQUE VERSUS THE TRANSFEMORAL SHEATH PROTECTED STENT TECHNIQUE

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Comparison of costs between two modes of implantation of Palmaz Schatz coronary stents: The transradial bare stent technique versus the transfemoral sheath protected stent technique.

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ABSTRACT

Rationale. Coronary Palmaz Schatz stent implantation is usually performed by using the sheath protected stent delivery system (SDS) via the percutaneous transfemoral route. However, downsizing of PTCA equipment made transradial coronary stenting feasible. Bare stent implantation, 6F technique, increased patient mobility, reduced vascular complications and reduced hospital stay may increase cost effectiveness of this novel technique.
Methods. Two well documented patient groups selected for elective single vessel and single lesion Palmaz Schatz stent implantation were retrospectively compared. Group A (transradial stenting; n=35) was compared to Group B (transfemoral stenting; n=25) derived from the Benestent population, included in our hospital. A comparison was made for 3 areas of interest: I. Procedural consumption of material (the number of guidingcatheters, guidewires, balloon-catheters and stents); II. Postprocedural need for diagnostic and therapeutic procedures for stent related complications; III. Duration of hospital stay. Differences between these subjects in Group A and B were translated to hospital costs.
Results. Although more guidingcatheters were used in group A (1.69 ± 0.87 versus 1.08 ± 0.28; p=0.001), the use of the SDS contributed importantly to higher material costs in group B (cost reduction in group A; 13%). Less patients in group A required diagnostic (2 versus 7; p=0.027) and therapeutic (0 versus 5; p=0.01) procedures for bleeding complications (cost reduction; 93%). Hospitalization in Group A was shorter (6.4 ± 4.7 versus 11.6 ± 9.9 days; p=0.005), caused by early and safe mobilization, less vascular complications and preprocedural adjustment on coumadin (cost reduction; 45%). Overall, the mean cost per patient in group A was 67% of these costs in group B.
Conclusion. Significant savings were realized with the transradial bare stent technique, by reduction of costs for angioplasty material, diagnostic and therapeutic procedures for stent related complications and hospital stay.

INTRODUCTION

Transfemoral artery coronary stent implantation with a sheath protected stent delivery system (Johnson & Johnson Interventional Systems, Warren, NJ) requires the use of large bore (8 or 9 French) guiding catheters. In combination with intense anticoagulation regimens this approach is associated with a high incidence of access-site related bleeding complications, often requiring additional diagnostic and therapeutic procedures and prolonged hospitalization (1,2,3,4). Miniaturization of balloon catheters made coronary angioplasty (PTCA) possible through 6 French (F) guiding catheters, with maintenance of means to improve suboptimal PTCA- results with perfusion balloons (5,6) and with coronary stents (6,7). Additionally, smaller arteries became suitable as entrysite for coronary angioplasty. Successful coronary angiography via the radial artery has been reported by Campeau in 1989 (8). More recently we described techniques for percutaneous transradial coronary angioplasty (9,10) and coronary bare stent implantation (11,12,13), with high procedural success rates and low vascular complication rates. The major advantages of the 6F transradial artery approach for stent implantation are the superficial course of the radial artery, allowing easy hemostasis and the

absence of major veins and nerves, excluding damage to these structures. These factors contribute to a low incidence of major entrysite complications and to increased patient comfort by immediate postprocedural mobilization. Additionally, the "under-over" principle can be applied with the bare stent technique by using one to two balloons; the first one serving for predilatation, stent delivery and secondary dilatations, and if necessary, a second one to optimize deployment. The traditional sheath protected technique usually requires three balloons: one for predilatation making passage of the delivery system possible, one for stent delivery (incorporated in the delivery unit) and an additional one for secondary dilatations. These basic differences in the two approaches should translate in a reduction of cost, in favor of the transradial technique. This study compares the procedural and inhospital costs of the generally applied transfemoral sheath protected stent technique and the transradial bare stent technique, in patients selected for elective single vessel, single lesion stenting.
Both study populations are compared in a non-randomized fashion. However, the study groups are derived from two prospectively studied and well documented populations: the transfemoral treated patients are derived from the Benestent study population (4), randomized to stent implantation in our center and the transradial treated patients from a prospective feasibility study to transradial coronary stenting.

METHODS

Study population
From March to November 1993, 35 consecutive patients underwent elective single stent implantation via the radial artery (Group A). These patients were compared with 25 patients who were randomized to stent implantation for the Benestent study in our department from June 1991 to May 1993 (Group B). Data concerning areas of interest were prospectively collected in both groups. Comparison between the groups however, was made retrospectively.

Areas of interest
A comparison was made for 3 areas of interest: (I) Procedural consumption of material (the number of guidingcatheters, guidewires, balloncatheters and stents). (II) Postprocedural need for diagnostic and therapeutic procedures for stent related complications. (III) Hospitalizationtime for both groups. Differences between these areas were translated to hospital costs in Dutch guilders (1 DFl: ± 0.6 US $). Cost of any procedure, includes material costs and utilization charges for personnel and equipment. The total cost for the procedure was determined by adding these costs to the charges for each hospital-day. No data on procedural time were available of the Benestent population, thus a comparison of catheterization laboratory resource utilization could not be made. Also, laboratory assessments after the procedure were not taken into account, because protocols for both groups showed marked differences; a less extensive pre- and postprocedural analysis was performed in group A.

Stent implantation
A. Transradial artery protocol

Catheterization, angioplasty and stent implantation
After local anesthesia of the skin with Xylocaine 2%, the radial artery was punctured with an Arrow® (Arrow International Inc. Reading, PA), 22 gauge radial artery catheterization set or with an 18 gauge arterial puncture needle. An 0.025 inch, 260 cm long guidewire was introduced through this system, followed by insertion of a 6 French, 10 cm long arterial introducer. A 6 French guiding catheter with an inner diameter of 0.060" (Scimed® Triguide™; Scimed Life Systems, Inc., Mineapolis, MN) or of 0.062" (Cordis® Petite™; Cordis Corp., Miami, FL) was selected with an appropriate curve, providing maximal backup support and coaxiality during angioplasty and stent implantation. Over a 0.014 inch intracoronary guide-

wire, a rapid exchange, low profile, compliant balloon catheter (Scimed® Express™; Scimed Life Systems, Inc., Mineapolis, MN) was positioned at the stenosis. The inflation pressure dependent variation of balloon diameter made a single balloon approach for predilatation and stent delivery possible. The stenosis was predilated in order to facilitate positioning of the stent loaded balloon at the lesion. The predilating balloon catheter was preferably used as stent carrier. A 7.3 mm or 15 mm Palmaz Schatz coronary stent was manually crimped on the balloon catheter. After delivery, the stent diameter was optimized by successive dilatations with higher inflation pressures or with larger balloon catheters.

Introducer sheath removal and hemostasis

In all instances, the arterial sheath was removed, immediately after withdrawal of the guiding catheter, followed by application of an occlusive tourniquet at the radial artery puncture site for a minimum of 30 minutes. Pressure was gradually released until hemostasis was obtained. A pressure bandage over the punctured artery was applied for 6 hours. Patients were not restricted to bed rest.

B. Transfemoral artery protocol

Catheterization, angioplasty and stent implantation

PTCA was performed via an 8F, 20 cm long introducer sheath. Super flow guiding catheters with an internal diameter of at least 0.079", were used in combination with a rapid exchange dilatation system and a 0.014" intracoronary guidewire. The lesion was predilated with an undersized balloon to facilitate passage of the stent delivery system. This system is a preassembled unit, containing a 5F sheath covered, 15 mm Palmaz Schatz stent, mounted on a polyethylene, compliant balloon catheter (balloon sizes; 3.0, 3.5 or 4.0 mm). The recommended maximal inflation pressures are 5.7, 6.2 and 6.0 atmospheres, respectively. The system was advanced over the extended guidewire to the obstructing lesion followed by stent delivery. Compared to the coronary artery diameter, the stent was slightly oversized by high pressure dilatations with larger balloons to optimize stent deployment.

Introducer sheath removal and hemostasis

After the procedure the arterial sheath was left in situ until the Activated Partial Thromboplastin Time (APTT) was less than 60 seconds. After sheath removal the groin was compressed manually, until hemostasis was achieved, followed by an compression bandage for 8 hours and an 24 hour immobilization period. In some patients hemostasis was achieved by insertion of collagen plugs (Vasoseal®).

Medical treatment

Immediately before and after stent deployment 200 microgram nitroglycerin was given intracoronary. Additional pharmacologic treatment was aimed at the prevention of thrombosis and spasm. Rheomacrodex 40, 100 cc/hour to a total of 1 litre, was started two hours before the procedure. Heparin 10.000 IU was administered through the arterial sheath after its insertion, followed by 5.000 IU for each hour the procedure lasts. According to the protocol, a second 10.000 IU bolus of heparin was given after stent- implantation in group B. In this group the heparin infusion was discontinued untill the APTT was under 60 seconds, before the sheath was removed. After 2 hours, heparinization was restarted by an intravenous loading dose of 5000 IU, followed by a heparin infusion, titrated to APTT's of 80-100 seconds, measured at 8 hours intervals. In group A the sheath was removed immediately after the procedure. A heparin infusion was started 3 hours following hemostasis after a loading dose of 3.000 IU. Acenocoumarol (Sintrom) was administered during 3 months, the dosage adjusted to maintain a TT (Thrombotest "QUICK") of 5 to 10% (INR $\geq$ 2.7). Heparin was stopped when the patient had 3 consecutive TT's in the therapeutic range. In group A, 5 patients (14%) were adjusted on coumadin, prior to admission. Additional treatment consisted of Dipyridamole

225 mg/day during 6 months, Acetosalicylic acid 300 mg/day during 6 months and Diltiazem 180 mg/day for 3 months.

Statistical methods

Values are expressed as mean ± standard deviation. Mean values in both groups were compared by the unpaired, two-tailed t- test. Incidence of complications, as well as the need for diagnostic and therapeutic procedures were compared by the Fisher's exact test. Differences with p-value less then 0.05 were considered to be significant.

RESULTS

Baseline clinical characteristics and vessel distribution are given in Table I.
In group A significantly more patients received a stent for venous bypass graft stenosis, which was considered to be an exclusion- criterium for group B.
In Group B, 2 patients did not receive a stent. In one patient it was not possible to predilate the stenosis. In another patient, cannulation of the right coronary artery resulted in an extensive dissection, which was treated conservatively. Both patients underwent elective coronary bypass surgery, several months after discharge. Two additional patients in group B developed subacute stent thrombosis, treated by acute repeat PTCA, followed by coronary bypass surgery. In group B, bleeding complications, requiring additional diagnostic or therapeutic procedures was encountered in 9 patients (36%) {vascular; n=7, hematuria; n=2} versus one patient with hematuria (3%) in group A (p=0.001). In this group however, 1 patient underwent a CT-scan of the brain for a transient ischemic attack. Another patient was treated for fever of unknown origin, prolonging hospital stay to 29 days. No patients in group A had an access-site related complication. In Table II the use of angioplasty equipment, need of additional diagnostic and therapeutic procedures for stent related complications and hospital stay per patient are displayed. These differences are translated to mean costs per patient in Table III.

Table I. Baseline clinical characteristics of patients with transradial bare stent implantation (group A) and with transfemoral sheath protected stent implantation (group B).

	Group A (n=35)	Group B (n=25)	P
Age	62±10 (44-83)	57±9 (38-69)	NS
Male	30 (86%)	21 (84%)	NS
CCS- class			
I	0 (0%)	0 (0%)	NS
II	2 (6%)	6 (24%)	NS
III	16 (46%)	13 (52%)	NS
IV	14 (40%)	4 (16%)	NS
Non-exertional	3 (8%)	2 (8%)	NS
Vessel			
VBG	11 (31%)	0 (0%)	0.002
LAD	11 (31%)	11 (44%)	NS
CX	4 (12%)	9 (36%)	0.03
RCA	9 (26%)	5 (20%)	NS

Table 1, continued

LAD	Left Anterior descending coronary artery
CX	Circumflex coronary artery
RCA	Right coronary artery
VBG	Saphenous vein coronary bypass graft

Table II. Use of angioplasty equipment, incidence of complications, diagnostic and therapeutic procedures and hospital stay after transradial (group A) and transfemoral (group B) coronary stenting.

	Group A (n=35)	Group B (n=25)	P
Material			
- Guiding catheters	59 (1.69±.87; range 1-4)	27 (1.08±.28; range 1-2)	0.001
- Guidewires	43 (1.23±.69; range 1-4)	26 (1.04±.20; range 1-2)	NS
- Extensionwires	0 (0.00)	23 (0.92±.28; range 0-1)	<0.001
- Balloncatheters	62 (1.77±.65; range 1-2)	48 (1.92±.49; range 0-3)	NS
- Bare stents	37 (1.06±.34; range 1-3)	0 (0.00)	<0.001
- SDS	0 (0.00)	24 (0.96±.35; range 0-2)	<0.001
Cardiac complications			
- Patients	0	2	NS
rePTCA	0	2 (0.08±0.28; range 0-1)	NS
CABG	0	2 (0.08±0.28; range 0-1)	NS
Bleeding complications			
- Patients	1	9	0.001
Other complications			
- Patients	2	0	NS
TIA	1	0	NS
Fever	1	0	NS
Diagnostic procedures for non- cardiac complications			
- Patients	2	7	0.027
- Total procedures	4 (0.11±0.53; range 0-3)	21 (0.88±1.72; range 0-6)	0.015
Ultrasound	1 (0.03±0.17; range 0-1)	14 (0.56±1.04; range 0-4)	0.005
Venous DSA	0	3 (0.16±0.47; range 0-2)	0.049
IVP	1 (0.03±0.17; range 0-1)	2 (0.08±0.28; range 0-1)	NS
Cystoscopy	1 (0.03±0.17; range 0-1)	2 (0.08±0.28; range 0-1)	NS
CT- brain	1 (0.03±0.17; range 0-1)	0	NS
Therapeutic procedures			
- Patients	0	5	0.01
- Total	0	7 (0.28±0.61; range 0-2)	0.009
Surgery	0	5 (0.20±0.58; range 0-2)	0.045
Collagen	0	1 (0.04±0.2 ; range 0-1)	NS
Compression	0	1 (0.04±0.2 ; range 0-1)	NS
Blood transfusions for bleeding complications			
- Patients	0	4	0.026
- Units	0	17 (0.68±1.84; range 0-8)	0.032

Table II, continued

Hospitalization			
- Days	223 (6.4±4.7; range 1-29)	291 (11.6±9.0; range 2-45)	0.005
- Median	6.0	8.0	

CABG	Coronary Artery Bypass Grafting
CT	Computerized Tomography
DSA	Digital Subtraction Angiography
IVP	Intravenous Pyelography
PTCA	Percutaneous Transluminal Coronary Angioplasty
SDS	Stent Delivery System
TIA	Transient Ischemic Attack

Area of interest I: Consumption of angioplasty equipment.
In group A more guidingcatheters were used (1.69 ± 0.87; range 1-4) compared to group B (1.08 ± 0.28; range 1-2) {p=0.001}, which reflects the difficulty to engage the coronary arteries in a stable and coaxial fashion with Judkins-type catheters via the right radial artery. Since in group A rapid exchange balloon catheters were used, no extension wires were required, versus 0.92 ± 0.28 in group B (p<0.001). The number of ballooncatheters (1.77 ± 0.65 and 1.92 ± 0.49) and stents (1.06 ± 0.34 and 0.96 ± 0.35) did not differ significantly. However, in group A only bare stents were used, whereas the more expensive stent delivery system in group B was used, which can be considered as a stent with an additional balloon. If the SDS is considered in this way, in group B 2.88 ± 0.67 balloons were used (p<0.001). Material costs in group A were reduced by 13% of the costs made in group B.

Area of interest II: Diagnosis and therapy for stent related complications.
In group B, 2 patients needed emergency repeat PTCA followed by coronary bypass surgery for subacute stent thrombosis, whereas no patients had a cardiac complication in group A (p=NS). More patients in group B (n=7) required a diagnostic procedure (total number of procedures 21; 0.88 ± 1.72; range 0-8) compared to group A (n=2) (total procedures 4; 0.11 ± 0.53; range 0-3) {p=0.027}. More patients in group B required bloodtransfusions (17 units) compared to group A (4 versus 0 patients; p=0.026). In group B, 7 vascular interventions were required versus none in group A (p=0.009). In the former group, 2 patients required 2 vascular operations and one patient a single operation. Another patient underwent percutaneous treatment of a pseudoaneurysm by transcatheter application of collagen and one patient underwent successful ultrasound guided closure of a pseudoaneurysm by prolonged compression. With respect to periprocedural diagnostic and therapeutic interventions for complications, cost reduction in group A was 93%, when repeat PTCA and coronary bypass surgery are not taken into account.

Area of interest III: Hopsitalization.
Patients in group A were discharged earlier (6.4 ± 4.7; range 1-29) compared to group B (11.6 ± 9.0; range 2-45) {p=0.005}. Cost reduction in group A by shorter hospitalization was 45%. In group A more patients were on coumadin before admission (n=5) and could be discharged after 1 or 2 days. In group B no patients were adjusted on coumadin prior to admission (NS).
Overall, the savings achieved (Dfl 4.636,72) by the transradial bare stent technique was 33% of the total costs for the transfemoral sheath protected stent technique. If costs for repeat PTCA and emergent bypass surgery in group B are not taken into account, mean cost per patient in group A was still Dfl 2.631,54 less than in group B (cost reduction; 22%).

Table III. Mean hospital costs per patient of transradial (Group A) versus transfemoral (Group B) coronary stenting.

		Group A (n=35)		Group B (n=25)	
	Price	Mean price per patient		Mean price per patient	
Material		**Mean**	**±SD**	**Mean**	**±SD**
- Guidingcatheters	*Dfl 323,00*	545,87	281,01	348,84	90,44
- Guidewires	*Dfl 335,00*	412,05	231,15	348,40	67,00
- Extensionwires	*Dfl 46,00*	0,00	0,00	42,32	12,88
- Balloncatheters	*Dfl 1809,50*	3202,82	1176,18	3474,24	886,66
- Bare stents	*Dfl 2780,00*	2946,00	945,20	0,00	0,00
- SDS	*Dfl 4350,00*	0,00	0,00	4176,00	1461,60
		7106,74	**2633,54**	**8389,80**	**2518,58**
PTCA utility costs	*Dfl 1117,36*	1117,36	0,00	1117,36	0,00
		8224,10	**2633,54**	**9507,16**	**2518,58**
Treatment for cardiac complications					
- rePTCA	*Dfl 5064,81*	0,00	0,00	405,18	1418,14
- CABG (same pts)	*Dfl 20000,-*	0,00	0,00	1600,00	5600,00
		8224,10	**2633,54**	**11512,34**	**9536,72**
Diagnostic procedures for complications					
- Ultrasound	*Dfl 122,50*	3,68	19,13	68,60	127,40
- Venous DSA	*Dfl 286,29*	0,00	0,00	45,81	134,56
- IVP	*Dfl 286,29*	8,59	48,67	22,90	80,16
- Cystoscopy	*Dfl 250,00*	7,50	42,50	20,00	0,00
- CT- brain	*Dfl 444,00*	13,32	75,48	0,00	0,00
		8257,19	**2819,32**	**11669,65**	**9948,84**
Therapeutic procedures					
- Surgery	*Dfl 1100,-*	0,00	0,00	220,00	638,00
- Collagen	*Dfl 785,-*	0,00	0,00	31,40	157,00
- Compression	*Dfl 122,50*	0,00	0,00	4,90	24,50
		8257,19	**2819,32**	**11925,95**	**819,50**
Blood transfusions for bleeding complications					
- Units	*Dfl 47,00*	0,00	0,00	31,96	58,81
		8257,19	**2819,32**	**1957,91**	**878.31**
Hospitalization					
- Days	*Dfl 180,00*	1152,00	846,00	2088,00	1620,00
	Total	**9409.19**	**3665,32**	**14045,91**	**2498,31**

Table III, continued

CABG	Coronary Artery Bypass Grafting
CT	Computerized Tomography
DSA	Digital Subtraction Angiography
IVP	Intravenous Pyelography
PTCA	Percutaneous Transluminal Coronary Angioplasty
SDS	Stent Delivery System
TIA	Transient Ischemic Attack

DISCUSSION

In previous studies costs of inhospital stay have been analyzed for patients who underwent elective angioplasty, directional angioplasty and coronary Palmaz Schatz stent implantation. Cost of coronary stenting turned out to be 103% higher when compared to conventional angioplasty (14). Caused by a longer hospital stay and increased utilization of resources, Cohen et. al. found total hospital charges 35-45% higher than for other interventional procedures (15). In this study costs for stenting were higher than for atherectomy due to the more frequent adjunctive use of conventional balloons. Additionally, the device itself was the largest single component of procedural cost. However, the stent technique applied was the conventional transfemoral, sheath protected approach, where large bore guiding catheters were used. No cost comparison has currently been made between this approach and the transradial stent technique. During a properly applied conventional technique, the target lesion is predilated, before the stent is delivered with the stent delivery system. In order to maximize the stent diameter, a secondary dilatation with high pressure oversized balloons is usually performed. By the transradial approach, only the bare stent technique can be applied, because the sheath protected stent delivery system and 6F guidingcatheters are not compatible. By using the predilatation balloon as the stent carrier, one balloon is saved. Oversizing can be performed by the same balloon or by a larger balloon if necessary.
More guidingcatheters were used in the patients treated via the radial artery. This is explained by the fact that most commonly used catheters are preshaped for the femoral approach. Since optimal backup support and coaxial alignment is required in order to achieve a successful stent implantation, meticulous care was addressed towards proper guiding catheter selection. Also, sharp primary and secondary angles in the guidingcatheter, may cause excessive friction between the stent-loaded balloon and the inner surface of the guidingcatheter. Allthough this has not resulted in stent dislodgement in our experience, sharp angled guidingcatheters (e.g. Amplatz- shapes) are avoided. For the right coronary artery and for venous bypass grafts, multipurpose shaped guiding catheters were most frequently used and for the left coronary artery the Voda- shape was selected.
At present it is known that coronary stenting by the conventional approach is associated with an important incidence of access-site related bleeding complications (1,2,3,4). In the Benestent study, a randomized trial comparing safety and efficacy of coronary stenting versus balloon angioplasty, the incidence of bleeding and vascular complications was 13.5%. In the patient population randomized to stenting in our department, a 20% incidence of major bleeding complications, requiring surgery or bloodtransfusions, was encountered. These complications, prolonged immobilization of the patient and the time it takes to adjust patients on coumadin, contribute significantly to a longer admission time.
The transradial technique on the other hand was not associated with major bleeding complications and immediate mobilization of the patient, together with preprocedural adjustment on coumadin made earlier hospital discharge possible.
The present study compares both techniques in two well documented patient populations. We demonstrated an important reduction in costs of angioplasty material (13%) in favor of the

transradial technique, despite the high number of guiding catheters used in this group. As expected, postprocedural cost reduction (93%) was established in the transradially stented patients, due to less diagnosic and therapeutic procedures for bleeding complications. A shorter hospital stay in group A resulted in an additional 45% cost reduction. Overall, the costs for transradial bare stent implantation were 67% of the costs for the conventional transfemoral technique. When eliminating extra costs associated with repeat PTCA and emergent bypass surgery (2 patients in group B), the transradial technique was still 22% cheaper than the sheath protected, transfemoral technique.

Study limitations.

The two study populations were compared in a non-randomized fashion, however, the study groups are derived from two prospectively studied and carefully documented populations: the transfemoral treated patients are derived from the Benestent study population (4), randomized to stent implantation in our center and the transradial treated patients from a prospective feasibility study to transradial coronary stenting.

This retrospective study shows differences in some baseline characteristics between the two different populations. The "ideal" character of the Benestent patients (de novo lesions in native coronary arteries in patients with stable angina) is in contrast with the more unfavorable baseline characteristics of the transradial group (unstable angina, venous bypass graft stenosis). Procedural success however was not significantly different in both groups. With 2 failed stent procedures, 2 subacute occlusions requiring repeat PTCA and bypass surgery and with 8 bleeding complications (5 major complications) out of 25 Benestent patients, we had a higher incidence of complications compared to the total Benestent study population. This means that for larger study populations the differences in costs between both techniques may be less outspoken. The lower incidence of complications in group A is not only determined by the radial artery approach. The transradial stent experience is from a later date, when more details on the pitfalls of coronary stenting were recognized and more attention was focused on optimalization of the final results and on the optimal timing of heparinization after sheath removal. Also, a reduction of costs, associated with the transfemoral approach, can be expected if bare stents would have been implanted via 6F transfemoral guiding catheters and if patients would have been adjusted on coumadin prior to the procedure. It can also be expected that stenting via the femoral artery, on minimized anticoagulation regimens with the conventional stent (16,17,18) or with heparin-coated stents (19) will also be associated with less bleeding complications. The impact of different hemostasis devices on the safety of transfemoral stenting, remains unclear. In our experience, we could not prevent bleeding complications with the Vasoseal, after coronary stenting (20). Carere et al. reported on a 18-33% of complications, associated with the use of this device after transfemoral coronary angiography and PTCA, including stents (21). These devices, and others such as pneumatic compression devices (22) and percutaneous suture devices (23), are having their price and will also add to the costs of coronary stenting. However, it was not the purpose of this study to compare costs of stenting via two different entry sites, but to compare two strategies; the traditional transfemoral sheath protected technique versus the novel transradial, bare stent approach. Another limitation is the incomplete analysis of true costs. Not all elements were taken into account such as laboratory costs, pharmacological costs, intensity of nursing care and physician charges. However, by analyzing the most important items with expected largest differences (angioplasty equipment, diagnostic and therapeutic procedures for complications and hospital stay) we were able to establish a realistic comparison between the techniques. Finally, we did not perform an analysis of costs for postdischarge complications, but no major differences are expected between both groups after successful stenting. Despite these short-comings, it can be concluded that, compared to the traditional stent technique, transradial coronary bare stent implantation reduces costs by a lower consumption of balloon catheters, a reduced incidence of entry site related complications and by a shorter hospitalization.

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CHAPTER 4.6.6

POTENTIAL SOLUTIONS

RADIAL ARTERY AS ENTRY SITE

Transradial artery coronary stent implantation

TRANSRADIAL PALMAZ SCHATZ CORONARY STENTING ON AN OUTPATIENT BASIS; RESULTS OF A PROSPECTIVE PILOT STUDY

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Transradial Palmaz–Schatz Coronary Stenting on an Outpatient Basis: Results of a Prospective Pilot Study

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ABSTRACT: Background: The applicability of Palmaz Schatz coronary stent implantation is limited by bleeding complications and prolonged hospitalization. Coronary stenting on an outpatient basis, may be the ultimate means to reduce costs of this treatment. Since bleeding and stent occlusion were infrequent complications in a group of 100 ambulatory patients who underwent stent implantation via the radial artery in our department, we performed a pilot study to determine the feasibility of using coronary stenting on an outpatient basis.
Methods: Patients selected for Palmaz Schatz stent implantation, were adequately adjusted on coumadin. At an INR > 2.5, stenting was performed via the radial approach. Based on pre–, post– and procedural criteria, considering clinical status, procedural course and outcome, absence of predictors for stent occlusion and of events during 4 to 6 hours observation, patients were considered candidates for same–day discharge. Heparin was administered only during the procedure. Immediately after the procedure, the arterial sheath was removed. Patients were mobilized and were discharged with a pressure dressing over the puncture site. Follow–up was performed on the next day, at 2 weeks and at one month.
Results: Between May and September 1994, 47 patients underwent Palmaz Schatz stent implantation via the radial artery. Of these, 27 remained hospitalized for reasons, considered to be incompatible with outpatient treatment. Twenty patients (CCS-class III and IV; n=17 (85%)) received 29 stents for 23 lesions, distributed in 21 vessels and were discharged the day of treatment. No cardiac or bleeding events were encountered within 24 hours. At 2 weeks follow–up, one patient was readmitted (day 4) because of a bleeding abdominal aortic aneurysm, requiring surgery. At 1 month follow–up, no bleeding, entry–site and cardiac complications were noted.
Conclusion: Since no complications were encountered (95% confidence interval; 0-17%) in the first 24 hours after optimal coronary stent implantation in patients with an adequate preprocedural level of anticoagulation, a larger feasibility study of outpatient coronary stenting will be undertaken.

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Elective implantation of Palmaz–Schatz coronary stents is very rarely associated with acute (< 24 hours) coronary incidents provided the stent is optimally expanded and is not placed in the presence of angiographic predictors of stent occlusion. This phenomenon may allow coronary stenting to be performed on an outpatient basis if

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the patient can be mobilized immediately after the procedure and if the risk for bleeding complications from anticoagulation is minimized.

Transfemoral artery implantation of metallic coronary stents has the hazard of bleeding complications during the postoperative course when the patient is receiving intense anticoagulation[1-3], even during prolonged bed-rest.

Stent implantation through 6 French guiding catheters via the radial artery has been demonstrated to be an effective means of reducing the risk of major bleeding complications[4-6] in patients who are not restricted to prolonged immobilization.

No ischemic complications of the hand were encountered, even in 3 patients (3%) with a post-procedural radial artery occlusion. During a feasibility study on transradial stenting, conducted in our department, hospital stay was limited to one day in 22 patients who were on a therapeutic level of anticoagulation. None of these patients developed major complications following the procedure and early after discharge. Thus with the transradial artery approach it is possible to implant a Palmaz-Schatz stent on an outpatient basis, which reduces costs and which increases patient comfort. We conducted a non-randomized, prospective, single center pilot study to explore the feasibility of transradial Palmaz-Schatz coronary stenting on an outpatient basis.

METHODS

Study population. Patients referred for elective stent implantation were pretreated on Coumadin® prior to admission. Most of these patients came directly from home or, in some instances, from the referring hospital, to the catheterization laboratory. At the start of the procedure, an INR was assessed. If an INR > 2.5 was achieved, the patient was asked to participate in this study. Patients were excluded who underwent stenting via the femoral artery.

Study population. In our department, stent implantation is performed by the radial approach if the Allen-test is normal in the right or left hand. Reasons to implant stents via the femoral artery are: requirement of 8F systems (Benestent study), bailout stent procedure for a failed transfemoral PTCA or a failed (previous) transradial attempt.

Also, stenting as bail-out procedure and stenting in patients who were in poor clinical condition were reasons to exclude patients from the outpatient protocol.

Outpatient triage. Based on preprocedural, procedural and post-procedural variables, a decisions was made to keep the patient hospitalized or to discharge the same day (Table 1).

Transradial stent implantation technique. Technique of transradial angioplasty and stent implantation[4,5] has been described in detail before. In brief, the right arm was abducted and the wrist hyperextended. After local anesthesia, the radial artery was punctured with an Arrow® 22-gauge radial artery catheterization set or with a Kimmal® needle. After appearance of pulsatile flow from the needle, an 0.025 inch, 260 cm long, J-shaped guidewire (Schneider®) was introduced through this system, followed by insertion of a 6 French arterial introducer. During ongoing expe-

Table 1. Arguments for prolonged hospitalized following stent implantation.

A. Preprocedural
1. Unstable angina (last attack and ECG-changes within 24 hours despite in nitroglycerin)
2. Suboptimal adjustment on coumadin (INR < 2.5)
3. Poor clinical condition
4. Urgent non-PTCA related indications for hospitalization, e.g., social circumstances.

B. Procedural
1. Transient closure
2. Resuscitation
3. Prolonged chest-pain
4. Persistent ECG-changes
5. Suboptimal result: distal stenosis or obstructing dissection, thrombus
6. Major side branch occlusion
7. Entry site complication
8. Failed transradial attempt

C. 6 hours observational period
1. All cardiac events
2. Bleeding complications
3. Non stent-related complications

rience, we preferred using a 23 cm, instead of 10 cm long Terumo® 6F introducer sheaths, to prevent radial artery spasm and to facilitate guiding catheter manipulations.

Meticulous care was directed towards optimal selection of the guiding catheter with respect to backup support and coaxial alignment. The Cordis® Petite™ 6F guiding catheter was preferred because of its large inner diameter (0.062 inch). For left coronary artery procedures, the Scimed® Triguide™ 6F Voda curve was frequently selected because of optimal support and alignment, despite a smaller inner diameter (0.060 inch). Later in the study, this curve also became available from Cordis® (Extra Backup™). We selected Scimed® Express™ balloon catheters for predilatation and stent delivery because of their low profile, ease of advancement over the guidewire and through the guiding catheter and because of the proper fixation of the stent, once crimped on the balloon. One or more 7 mm, 10 mm or 15 mm Palmaz Schatz coronary stents (Johnson and Johnson Interventional Systems, Warren, New Jersey) were used. After delivery, the stent diameter was optimized by successive dilatations with higher inflation pressures or with larger balloon catheters of intermediate compliance [Schneider® Magical Speedy™ (20 mm) or Chubby™ (10 mm)]. Procedures were performed by two operators (FK and GJL).

Medical treatment. Elective patients were pretreated with coumadin, at least one week before the procedure. The INR was assessed just prior to the procedure. At an INR > 2.5, the patient received 10,000 IU heparin after sheath insertion and Acetosalicylic acid 500 mg intravenously. No heparin was given after the procedure.

Introducer sheath removal and hemostasis. The arterial sheath was removed immediately after withdrawal of the guiding catheter, followed by application of an occlusive tourniquet at the radial puncture site for a minimum of 30 minutes. Pressure was gradually released until hemostasis was obtained. A pressure dressing over the punctured artery was applied for 6 hours. Patients were encouraged to mobilize, and advised to restrict movements of the wrist joint.

Predischarge examinations. The clinical status of the patient was monitored by a physician and the radial artery was examined for adequate hemostasis and the presence of pulsations.

A new pressure dressing was applied, followed by application of a sling supporting the forearm. Written instructions were given to the patient, followed by oral explanations. The patient was advised to remove the pressure bandage the next day. Prior to discharge the patient was instructed on the method for achieving hemostasis by applying local pressure, in case of a puncture site bleeding. In case of uncontrollable bleeding or other emergency situations, patients were instructed to contact the general practitioner, the cardiologist, the first aid department of our hospital, the 24–hour service of our cardiology department or one of the available alarm telephone numbers.

Endpoints. A successful outpatient treatment was defined as an uncomplicated course within the first 24 hours after the stent procedure. A successful short–term outcome after coronary stenting was defined as an uncomplicated course in the first month after discharge. Follow–up was considered uncomplicated if none of the following endpoints occurred: death, acute myocardial infarction, need for coronary artery bypass grafting, need for PTCA of the stented coronary artery, angina caused by stent restenosis or occlusion and any bleeding requiring hospitalization. Occlusion of the radial artery was considered to

Table 2. Baseline characteristics

	N	%
No. patients	20	
Male gender	18	(90%)
Age (years)	63 ± 9	(range 45-76)
Exertional angina:		
CCS II	3	(15%)
CCS III	10	(50%)
CCS IV	7	(35%)
Prior myocardial infarction	11	(55%)
Prior bypass surgery	7	(35%)
Prior PTCA	8	(40%)
Hypertension	5	(25%)
Diabetes mellitus	3	(15%)
Cholesterol ≥ 6.5 mmol/1	3	(15%)
Smoking history	10	(50%)
Family history	9	(18%)

Table 3. Angiographical data

	N	%
Stented vessels (n=21)		
LAD	4	(19%)
LCX	4	(19%)
RCA	7	(33%)
VBG	5	(24%)
Intermediate branch	1	(5%)
Lesion morphology N=23)[7]		
Type A	5	(22%)
Type B	10	(43%)
Type C	8	(35%)

LAD = left anterior descending coronary artery; LCX = Left circumflex coronary artery; LM = Left mainstem; RCA = Right coronary artery; VBG = Venous bypass graft.

be a major event if the forearm or hand showed signs of ischemia (e.g., functional disability by claudication, necrosis, surgical recanalization).

Follow-up. The day following discharge and after 2 weeks, the patient was interviewed by telephone. Patients were questioned about the occurrence of any complications or discomfort. Questions from the patient were addressed during this same interview.

At one month follow-up, the patient was seen and screened for entry-site-related complications and cardiac complications. Radial pulse was also examined by palpation.

Statistical analysis. Values were expressed as mean ± standard deviation.

RESULTS

Between May and September 1994, 47 patients underwent Palmaz Schatz coronary stent implantation via the radial artery. Of these, 27 patients were considered to be unsuitable for treatment on an outpatient basis because of one or more of the following reasons: suboptimal adjustment on oral anticoagulation (n = 16; 59%), prolonged angina and/or persisting ECG changes during the procedure (n = 3; 11%), stenting after failed PTCA (n = 3; 11%), residual dissection (n = 2; 7%), unstable angina immediately prior to stent implantation (n = 1; 4%). The remaining 20 patients, treated on an outpatient basis underwent stenting for de novo lesions in native coronary arteries (n = 10; 50%), native coronary artery restenosis after previous PTCA (n = 5; 25%) and venous coronary bypass graft stenosis (n = 5; 25%). Baseline clinical characteristics, angiographical data and quantitative angiographical data of this group are shown in Tables 2, 3 and 4, respectively.

Procedural results. Stent implantation was successful in all patients. In 6 patients, multiple stents were implanted for long lesions (n = 3), multiple lesions (n = 2) and for a dissection after predilatation of the stenosis (n = 1). Diameter stenosis improved from 70 ± 16% to 9 ± 7%. In one patient a type B dissection, parallel to the stent was visible. No residual obstructions could be detected by digitized coronary angiography.

Clinical observation. Effective hemostasis was obtained within 1 hour in all patients. All patients were discharged before the evening of the day of coronary stent implantation, after an uneventful observation period. However, 4 patients coming directly from a referring hospital were not discharged home, but to their clinics for various reasons. For 3 of these patients, same-day-discharge had not been arranged with relatives. These patients remained for 1 night in their referring clinic. One patient needed further evaluation of mild renal failure. Since these patients, according to our criteria were suitable for outpatient treatment but were not admitted to our clinic, they were included in this study.

Table 4. Quantitative coronary angiography

	Baseline		Post stenting	
	Mean ± SD	Range	Mean ± SD	Range
Reference diameter (mm)	3.4 ± 0.4	2.8-4.4	3.7 ± 0.5	2.9-4.8
Minimal lumen diameter (mm)	1.0 ± 0.5	0.3-2.4	3.4 ± 0.4	2.9-4.4
Diameter stenosis (%)	70 ± 16	32-92	9 ± 7	0-20

24–Hour follow–up. None of the 20 patients had bleeding from the radial artery puncture site. No cardiac complications were encountered.

14–Day follow–up. Two patients were readmitted to our hospital. One patient had an aneurysm of the abdominal aorta requiring vascular surgery and was admitted 4 days after stent implantation with signs of bleeding from this aneurysm. This was successfully operated on the same day. This patient underwent stent implantation for severe anginal complaints caused by a stenosis in the circumflex coronary artery. Since the right coronary artery was occluded and left ventricular function (and anterior wall motion) was severely compromised, the LCX was considered to be the last remaining vessel. Coronary angioplasty was required before any operation for the aortic aneurysm could be undertaken. The patient was given Coumadin for 2 months. No additional anticoagulants, except for dipyridamole, were added to his medication. Therefore, this condition was not considered to be related to the stent implantation. The second readmitted patient had anginal complaints on the 11th day following stenting. Coronary angiography revealed a patent stent and no significant stenosis in other coronary arteries. The other patients were free of bleeding and cardiac complications.

One–month follow–up. At one month follow–up, no bleeding or cardiac complications were noted. One patient with significant coronary artery disease in non–treated and inoperable coronary arteries still had angina, but was functionally improved. None of the patients had complaints of disability of the hand. No signs of ischemia were noted. In all patients the radial artery was palpable at physical examination.

DISCUSSION

Coronary angioplasty is usually performed based on clinical indications. A major reason to keep the patient under clinical observation is the risk for acute reocclusion of the treated coronary vessel. The incidence for acute closure after balloon angioplasty was 7.5% in the early NHLBI PTCA registry (1977-1981)[8] and 6.8% in the second NHLBI PTCA registry (1985-1986).[9] In a more recent survey from Myler et al., the incidence was 4.9%.[10] This complication usually requires an immediate attempt to obtain restoration of flow by repeat PTCA, coronary stenting or emergency bypass surgery. The other major reason to keep the patient hospitalized is to limit mobility in order to reduce the risk for an access site related bleeding complication.

Since the number of patients undergoing coronary angioplasty is still increasing, there is a need to reduce costs since resources are limited. In centers with high case loads, the restricted number of available hospital beds may pose a problem. Coronary angioplasty on an outpatient basis may offer a solution to this problem.[11] Early mobilization after sheath removal may additionally be associated with increased patient comfort.

The ideal combination of requirements for outpatient coronary angioplasty should contain the following elements: probability of high procedural success rates, no risk for acute coronary artery closure, minimal risk for access site related bleeding complications and the ability to immediately mobilize the patient.

Implantation of Palmaz Schatz coronary stents is very rarely associated with acute stent occlusion (within 24 hours) if the stent is optimally delivered and if no predictors of stent thrombosis are present. From several early single center and multicenter series, no acute stent thromboses were reported.[1,12,13] Acute stent occlusion was not observed in an angiographic follow–up study of Kimura et al.[14] Stenosis diameter in the stent group was stable in the interval between stent implantation and the following day. No acute stent occlusion was encountered in the more recent Benestent[3] and the STRESS[2] studies, where patients were randomized to either balloon angioplasty or to stent implantation. However, subacute stent occlusion is a complication that usually occurs in the first week after stenting. With improved patient selection and by optimizing stent implantation techniques, the complication rate has fallen from high rates in the early experience after bailout stenting[15] to low rates in a later series. In a recent report on Palmaz–Schatz stent implantation in venous bypass grafts[13] no stent thrombosis was encountered. Low incidences of subacute stent thrombosis are reported after ultrasound controlled stent implantation (0%)[16] and even after stenting with subcutaneous heparin, combined with platelet inhibitors (0%).[17,18]

In our recent experience with 100 patients after transradial stent implantation, no stent occlusion

was encountered in electively treated patients (in press, *American Heart Journal*). Since an optimal result after stent implantation may help minimize the risk of acute vessel occlusion, a major prerequisite for outpatient angioplasty is to place patients on adequate levels of oral anticoagulation prior to the procedure.

Access site–related bleeding complications are the main hazard of coronary stenting in patients receiving complex anticoagulation regimens. By using smaller guiding catheters, we have demonstrated the feasibility of coronary stenting via the radial artery with downsized PTCA equipment. In 100 patients, one patient developed subcutaneous bleeding of the radial artery requiring surgical decompression of the hematoma. By immobilizing the hand with a supporting sling, risk for bleeding can further be reduced. With appropriate instructions, most patients are able to address a bleeding radial artery themselves. If after an observation period of 6 hours, no access site–related bleeding occurred, we consider hemostasis to be safely established. Together with the immediate mobilization of the patient after the procedure, the second and third requirements for outpatient coronary angioplasty are also met.

A careful patient selection, based on a triage, was performed before the decision was made to discharge the participating patients on the same day. This triage contained general criteria, making outpatient treatment after successful stent implantation impossible (e.g., poor clinical status, social circumstances, patient compliance, prolonged chest–pain with a good stent results, etc.) and generally accepted risk factors for stent thrombosis such as the presence of a distal obstructing lesion[19], intracoronary thrombus[19] and suboptimal anticoagulation.[1]

If this triage resulted in no reason for hospitalization, we used any complication during a post–procedural observation period as a final reason to keep the patient under clinical observation.

In the case of same–day–discharge, extensive information was given to the patient to optimize the safety of this new approach. It should be acknowledged that a minor bleeding in a hospital may turn into a major problem when the patient is at home. Therefore, we have kept the pressure dressing in place for 24 hours. No entry site bleeding and no cardiac complications were encountered early after discharge. Major concern on a stent thrombosis is addressed beyond the first 24 hours. Although stent thrombosis is a serious event frequently leading to myocardial infarction, the low incidence of this complication in patients on an adequate level of anticoagulation after an optimal stent result does not justify keeping ambulatory patients under prolonged clinical observation.

Study limitations. Only a small number of patients are described in this study. Of the 47 patients selected for transradial stenting, a minority were considered suitable for this outpatient protocol. Since no experience on outpatient stenting is currently available, we carefully defined exclusion criteria based on current literature on increased risk for occurrence of stent thrombosis. However, the most common reason to exclude patients was an inadequate level of oral anticoagulation. This policy may be changed in the near future by treating patients with potent antiplatelet medication only.

The small number of patients studied does not allow outpatient stenting to be recommended on a large scale. With a sample size of 20 patients without a bleeding or cardiac complication within the first 24 hours, the 95% confidence interval for the absence of complications runs from 0 to 16.8%. By expanding this experience, we will be able to report on the results of a larger study in the near future.

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CHAPTER 4.7

POTENTIAL SOLUTIONS

HEPARIN COATED PALMAZ SCHATZ CORONARY STENTS

IMPLANTATION OF HEPARIN COATED PALMAZ SCHATZ STENTS IN HUMAN CORONARY ARTERIES: PROCEDURAL AND CLINICAL RESULTS OF THE BENESTENT-II PILOT STUDY

The Benestent-II study group

Implantation of Heparin coated Palmaz Schatz stents in human coronary arteries: Procedural and Clinical Results of the Benestent- II pilot study

The Benestent- II study group

INTRODUCTION

The Benestent-I trial, a multicenter randomized study comparing the safety and efficacy of primary Palmaz Schatz stent implantation with balloon angiopasty (PTCA) in patients with stable angina and a de novo lesion in a native coronary artery, demonstrated that eventfree survival in patients who received a stent was higher compared to patients who underwent PTCA (80% versus 70%)(1). This was largely due to a reduction in repeat revascularization in patients who were treated with a stent by significantly reduced restenosis rates in this group (22% versus 32%). However, the incidence of bleeding complications (13.5%) and subacute thrombosis (3.5%) after stenting resulted in considerable longer hospitalization (8.5 days) than following balloon angioplasty (3.1 days).
A heparin coated stent has been developed, in order to improve the clinical results of coronary stenting by minimizing the risk for thrombotic stent occlusion and by reducing anticoagulant therapy. The Benestent-II pilot study is an open, multicenter, non-randomized, prospective registry, designed to evaluate the safety of elective implantation of a heparin-coated Palmaz Schatz stent in a patient population comparable to that enrolled in the Benestent-I study.

METHODS

Study design

Following stent implantation, heparin was reinstituted in a step-wise fashion. The study consisted of four phases in which a total of 202 patients were treated with a single stent (51, 50, 51 and 50 patients in each of the 4 phases). Heparin infusion was started 6, 12 and 36 hours after sheath removal in the first 3 respective phases. In phase 4, no heparin or coumadin was given, but patients were treated with aspirin and ticlopidine.
The decision to proceed with the study from the one phase to the next was made on the basis of a predetermined incidence of (sub-)acute thrombotic stent occlusion. If there were 3 or more incidents of subacute stent thrombosis in phase I (based on a 3.5% angiographically demonstrated subacute thrombosis rate in Benestent-I), the study had to be abandoned. Were there less then 3 subacute occlusions, phase II was started, and so on to phase IV.

Objectives

Primary endpoints included incidence of (sub-)acute stent occlusion, location and severity of bleeding complications during hospital stay and within 30 days of implantation. The occurrence of all cardiac and non-cardiac events during the same period (death of all causes, myocardial infarction, repeat revascularization procedures) was recorded.
Secondary objectives were the efficacy of the procedure (symptom-free and event-free survival at 6 months, freedom of death, myocardial infarction or repeat interventions) and changes in stenosis geometry, assessed by quantitative coronary angiography immediately after stent implantation and at 6 months.

Patient selection

Patients with stable angina, caused by a de novo lesion in a native coronary artery, were recruited for this study if there were no contraindications for anticoagulation or antiplatelet therapy or coronary bypass surgery. The lesion had to be located in a vessel of at least 3 mm in diameter and the lesion length was required to be less than 15 mm. Other anatomical con-

traindications were lesions in or distal from a sharp bend, or at a bifurcation of an important sidebranch (≥2.5 mm), ostial lesions and the presence of intracoronary thrombus. Also a lesion in a grafted coronary artery was an exclusion criterion.
The study was performed according to the principles of the Declaration of Helsinki. Oral or written informed consent was obtained from all patients.

Stent implantation technique
Stent implantation was performed via the femoral approach. The stent was delivered by the Stent Delivery System (SDS), a preassembled unit, containing a, 5F sheath covered, 15 mm heparin-coated Palmaz Schatz stent, mounted on a 3,0, 3.5 or 4.0 mm compliant polyethylene balloon catheter.

Medical regimen
Commencing the day before the procedure, all patients received 250-500 mg of aspirin daily and dipyridamole 75 mg 3 times a day. This medication was continued for 6 months.
Diltiazem 120 mg bid was continued until hospital discharge. An infusion of Dextran (1000 ml) was given, the first 500 ml at 100 ml/hr, the second 500 ml at 50 ml/hr.
In the first 3 phases, coumadin was given from the day of stent impantation for a period of 3 months. Heparin was administered as a bolus dose of 10.000 IU at the start of the procedure and reinstituted as continued infusion 6 h (phase 1), 12 h (phase 2) and 36 h (phase 3) after removal of the arterial sheath. Sheath removal took place when the aPTT had fallen to below twice the normal value (normal range 30-40 secs). Heparinization was gradually decreased when the INR (international normalized ratio) was within the therapeutic range (2.5 - 3.0) for at least 36 hrs.
In phase 4, patients received ticlopine 250 mg bid for 1 month, starting the day before the procedure. In this phase coumadin was not given and heparin 10.000 IU was administered only during the procedure.

Quantitative Coronary Analysis
The angiograms were analyzed at the core laboratory (Cardialysis, Rotterdam, the Netherlands) by the Cardiovascular Angiography Analysis System. To standardize the method of data acquisition and to ensure reproducibility of the angiograms performed after the intervention and at follow-up, measurements were made according to previously described methods.

Statistical analysis
Continuous variables are expressed by means ± SD. A p-value of < 0.05 was considered significant.

RESULTS

Between February and December 1994, 207 patients were included in the Benestent-II pilot study. Fifty-one, 55, 51 and 50 patients were enrolled in phases I-IV respectively.
In phase I, 2 patients received 2 stents in order to optimize the angiographical result. In phase II, 5 patients were excluded from further analysis, as they did not receive a stent. In 4 patients the SDS could not cross the lesion. In one of these patients, the ostium of the right coronary artery dissected, followed by acute surgery. This patient died postoperatively by intractable arrhythmias. In 2 other patients there was a problem with removal of the SDS- sheath. One patient could not be stented and in the other, a "bare" heparin coated stent was implanted. In phases III and IV, all allocated patients were evaluable. In phase IV, however, one "bare" heparin-coated stent was implanted, as the lesion was unable to be crossed with the SDS.

Four patients received 2 stents. Baseline clinical characteristics and lesion characteristics are displayed in Tables 1 and 2 respectively. For comparison, data on stented patients, participating in the Benestent- I study, are displayed in both tables.

Table 1. Baseline characteristics

	Benestent-I (n=225)	**Phase I (n=51)**	**Phase II (n=50)**	**Phase III (n=51)**	**Phase IV (n=50)**
Male	80%	88%	71%	82%	88%
Age (yrs)	57±9	59±10	58±10	59±10	58±10
	%	%	%	%	%
CCS I	4	4	9	6	5
CCS II	32	45	37	30	42
CCS III	48	33	41	9	23
CCS IV	6	2	0	4	11
Mixed	34	20	31	32	28
MI	20	10	23	34	23
CABG	0	6	2	4	2
PTCA	2	6	6	6	5
Diabetes	7	8	10	6	7
Hypertension	31	24	35	26	30
Cholesterol	35	31	46	34	30
Smoker					
-previous	46	39	33	23	51
-current	24	20	29	38	26

CABG	Coronary artery bypass grafting
CCS	Canadian Cardiovascular Society
MI	Myocardial infarction
PTCA	Percutaneous transluminal coronary angioplasty

Procedural data

During the course of the study, on line quantitative coronary angiography (QCA) became increasingly used, with 45%, 63%, 67% and 67% of cases during the 4 phases respectively. In phases I-IV, 10%, 8%, 20% and 8% of clinics respectively, used intravscular ultrasound to guide the stent procedure. Post stent dilatation in order to optimize final results were applied in 80%, 88%, 86% and 94% in the 4 phases respectively. Normal inflation pressure was used in 37%, 12%, 22% and 22% whereas pressures over 12 atmospheres were applied in 43%, 76%, 65% and 78% (Figure 1). In all groups, a mean of 2.8 devices (stent included) were used in order to come to achieve an acceptable final result. Maximum balloon diameter increased from 3.45 ± 0.40 mm to 3.54 ± 0.37 mm, 3.62 ± 0.43 mm and 3.64 ± 0.42mm in the 4 respective phases. In Benestent- I, mean maximum balloon diameter was 3.40 ± 0.40 mm.

Acute angiographic results

In table 3 data on pre- and postprocedural reference diameter (RD), minimal luminal diameter

Table 2. Lesion characteristics

	Benestent-I (n=225)	Phase I (n=51)	Phase II (n=50)	Phase III (n=51)	Phase IV (n=50)
	%	%	%	%	%
Concentric	49	27	41	22	19
Eccentric	51	63	53	74	75
Tandem	1	6	4	0	2
Multiple irregularities	7	4	2	4	4
Calcified	11	8	2	11	11
LAD	65	51	55	61	62
LCX	14	8	16	10	10
RCA	21	41	29	29	28
TIMI 0	1	0	0	0	0
TIMI I	1	4	2	2	2
TIMI II	11	10	8	9	9
TIMI III	86	86	90	89	89

LAD Left anterior descending coronary artery
LCX Left circumflex coronary aretry
RCA Right coronary artery
TIMI Thrombolysis in Myocardial Infarction

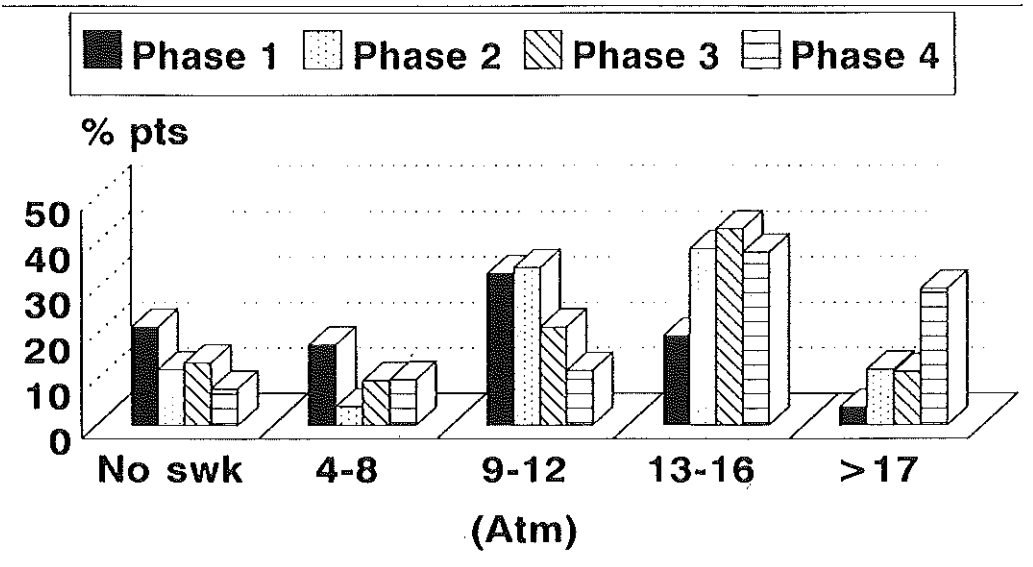

Figure 1. Distribution of maximal pressure during post stent dilatations.

(MLD) and diameter stenosis (DS) are given. When compared to Benestent-I, a trend towards selection of patients with a larger RD was detectable (3.00, 3.17, 3.06, 3.22 and 3.17mm respectively) as well as an increase in MLD post- stenting (2.51, 2.76, 2.75, 2.79 and 2.74mm). From phases I-IV, RD increased from a preprocedural value of 3.16 ± 0.41 mm to 3.38 ± 0.37 mm. (figure 2). A preprocedural RD less than 3.0 mm was encountered in 39% of the 202 patients, and a RD<2.75 mm in 16% and a RD<2.5 mm in 4%. A final RD of < 3.0 and < 2.75 mm was accepted in 12% and 5% of patients respectively.
In figure 3 and 4 cumulative frequency curves of MLD and RD are represented for Benestent-I and the 4 phases of Benestent-II. The final MLD was larger in Benestent-II and an improved final DS was obtained.

Table 3. Acute angiographic results

	Benestent-I (n=225)		**Phase I (n=51)**		**Phase II (n=50)**		**Phase III (n=51)**		**Phase IV (n=50)**	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
RD (mm)	3.00	3.17	3.17	3.41	3.06	3.32	3.22	3.42	3.17	3.36
MLD (mm)	1.07	2.51	1.11	2.76	1.09	2.75	1.13	2.79	1.07	2.74
DS (%)	64	21	65	19	65	17	65	18	66	18

DS Diameter Stenosis
MLD Minimal Luminal Diameter
RD Reference Diameter

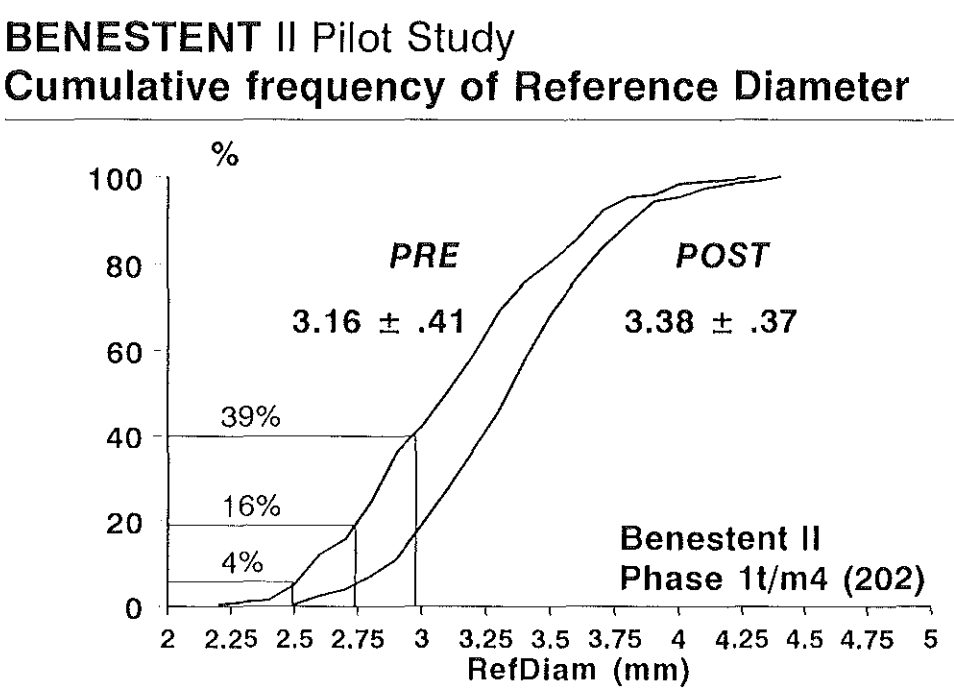

Figure 2. Cumulative frequency of RD in Benestent- II Pilot Study

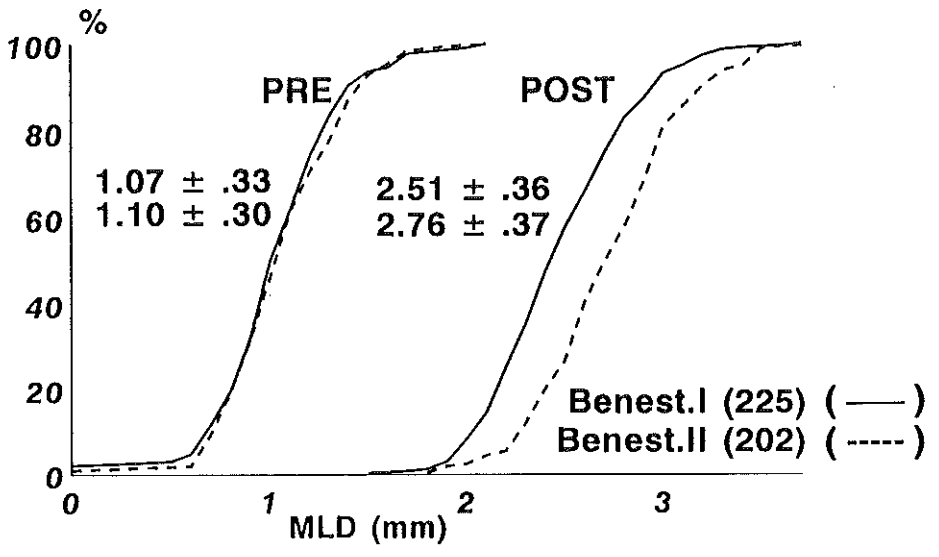

Figure 3. Cumulative frequency of MLD in Benestent-I and II

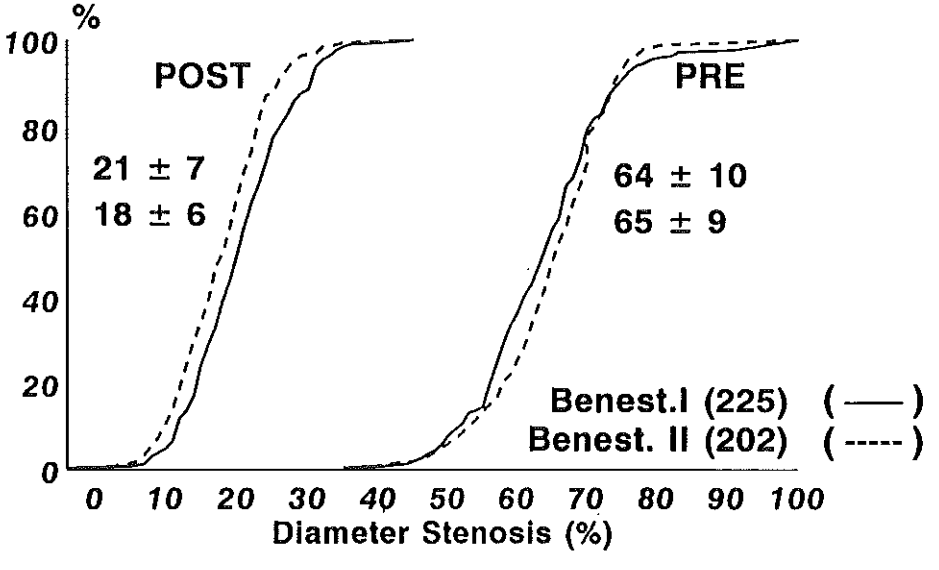

Figure 4. Cumulative frequency of DS in Benestent I and II

Clinical outcome during the in-hospital phase

Stent thrombosis was not encountered in this pilot study. Table 4 summarizes clinical events ranked in the following order; death, intracranial hemorrhage or CVA, Q- wave and non Q wave myocardial infarction, urgent CABG, elective CABG and rePTCA. In phase 2, 1 patient died after a failed attempt to deploy a stent, as mentioned above. A cardiac enzyme rise (CPK:349 [n=25-190]) was detected in one phase I patient, without signs of myocardial ischemia. In phase I and II, an additional bailout stent had to be implanted in 2 patients in order to cover a distal dissection. All patients were free of cardiac events during hospitalization, except for 2% in phase II. Major bleeding complications showed a trend to decrease in the respective phases (figure 5). Bleeding complications requiring therapy fell from 13.6% in Benestent- I to 7.9%, 4.1, 4.0% and 0% in the respective 4 phases of the pilot study. Hospital stay was 8.5, 7,4, 6,1, 7.0 and 3.0 days in the different study groups.

Table 4. Ranking of clinical events for Benestent- I and II

	Benestent-I	**Phase I**	**Phase II**	**Phase III**	**Phase IV**
	(n=225)	**(n=51)**	**(n=50)**	**(n=51)**	**(n=50)**
	%	%	%	%	%
Death	0.0	0.0	1.8	0.0	0.0
ICH/CVA	0.0	0.0	0.0	0.0	0.0
Q MI	1.9	0.0	0.0	0.0	0.0
non Q MI	1.5	0.0	0.0	0.0	0.0
Urgent CABG	1.9	0.0	0.0	0.0	0.0
Elective CABG	1.2	0.0	0.0	0.0	0.0
Re-PTCA	0.4	0.0	0.0	0.0	0.0
None	93	100	98	100	100
Subacute occlusion	3.5	0.0	0.0	0.0	0.0

CABG	Coronary artery bypass grafting
CVA	Cerebrovascular accident
ICH	Intracranial hemorrhage
PTCA	Percutaneous transluminal coronary angiography
Q MI	Q- wave myocardial infarction

DISCUSSION

The most important problems associated with the use of metallic coronary stents are mechanical rigidity and thrombogenicity, requiring complex anticoagulant treatment (2,3). Multi-drug anticoagulation is associated with unacceptable high access-site related rate of bleeding complications, if the femoral approach is used (1,4).

From the Benestent-I study it was learned that the positive effects, in terms of event-free survival were partially negated by costs of the stent itself, a prolonged hospital stay and additional costs related to the bleeding complications.

In order to further improve the clinical results of coronary stenting, attention is directed to coating the stent with material which would minimize the risk of abrupt stent closure and thereby allow a reduction in anticoagulant therapy. To that purpose a heparin-coated stent has been developed.

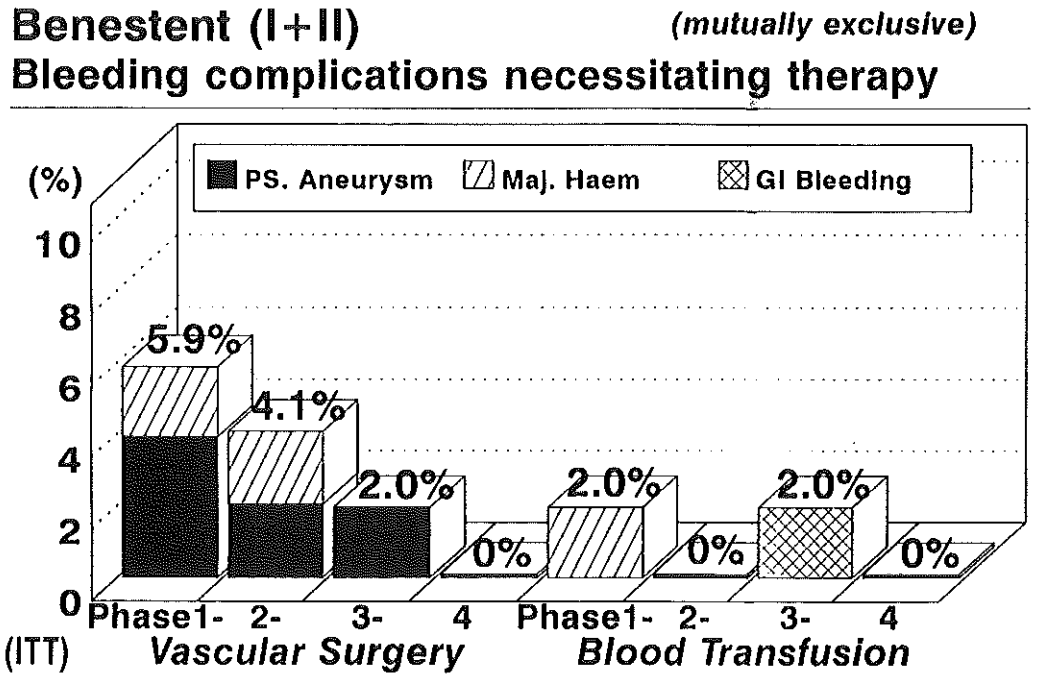

Figure 5. Incidence of bleeding complications requiring therapy.

Principles of heparin-coating.

Blood compatibility is a critical requirement for intravascular devices, since contact of blood with a foreign surface will commonly result in deposition and activation of plasmaproteins, platelets and other cellular elements, leading to thrombus formation. Over the last decades. there has been intensive research in the area of blood-compatible materials for non-coronary purposes (5). Instead of introducing a foreign mateial directly into a blood vessel, material surface modifications with improved properties with regard to blood and tissue compatibiility appears to be a promising approach. It has been shown that heparin-like molecules with anti-coagulant activity are synthesized on the luminal surface of endothelial cells (6,7). Indeed the endothelium plays an important part in the activation of thrombin and possibly other coagulation factors. Not unexpectedly therefore, heparin has been one of the most extensively explored substances for adsorbtion or binding to the surfaces of biomaterials. Heparin-coated surfaces have been evaluated in various types of devices where thromboresistance might be of particular clinical value, e.g. arteriovenous shunts, catheters, arterial filters, oxygenators, cardiopulmonary bypass circuits and vascular endoprosteses (8-12).

The principal anticoagulant mechanism of heparin is its interaction with antithrombin-III, accelarating the inactivation of thrombin and other coagulation factors. It has been shown that the active site of heparin contains a specific carbohydrate sequence (13-15). Obviously, when the heparin molecule is modified by the process of surface coating, it is essential that the active sequence responsible for anticoagulation remains unaltered. The simplest solution for binding heparin to a surface is adsorbing a heparin solution to the biomaterial surface (16). A problem with this type of coating is the lack of control of the rate of release. The heparin molecule contains a large number of negatively charged groups and may therefore be ionically or electrostatically bound to surfaces with positive charges (17-19). Another principle is to incorporate heparin molecules into a polymer, either to make heparin a permanent component of the polymer, "surface-grafter" heparin (20), or to provide a controlled release of heparin upon introduction into the blood stream (21,22). Since heparin is a higly charged and hydrop-

hillic polymer, the binding has to prepared by pretreatment of the surface to be coated with reactive groups ("functionalising"). In the early development of heparin-coatings, a reduction of heparin activity was frequently observed when the molecules were covalently attached to the surface, probably due to alteration of the active carbohydrate sequence during the linking process (23). This problem was circumvented if heparin was coupled by end-point attachment (24,27). The first step in this procedure is partial degradation of heparin with nitrous acid, creating reactive aldehyde groups in the reducing terminal residues. In 1983 it was shown by Larm et al. that heparin fragments could be immobilized by end-point attachment on materials coated with polyethylenimine (24). The aldehyde group was subsequently coupled to the animated surface by reductive animation. By this method, the active carbohydrate sequence of the heparin molecule can be preserved functionally intact throughout the coupling reaction.
In addition to being compatible with the plasma coagulation system, a thromboresistant surface should not promote adhesion and activation of platelets and leucocytes. Since heparin has been reported to induce platelet activation (26), this consequence might be expected with surface immobilized heparin as well. However, it has been shown that in comparison with uncoated material the surface with end-point attached heparin on a high molecular weight polyamine stabilized with glutaraldehyde, was highly compatible with platelets as well as granulocytes and macrophages (27,28).
The principle of perpendicularly oriented, end-attached, covalently bound and immobilized heparin molecules on a polymer surface (Carmeda Bioactive Surface, Carmeda AB, Stockholm) was considered to be the best technique for coating of coronary stents. A new "CH5" coating, a special form of the Carmeda Bioactive Surface, was used, allowing higher heparin activity on the stent surface.
In an in vitro model, ^{111}Indium labeled platelet attachment to uncoated and heparin-coated stents was measured. Platelet attachment to the coated stents was reduced by about 95%.
In an animal study, heparin-coated and uncoated Palmaz Schatz stents were implanted in the left anterior descending coronary artery of 40 non-atherosclerotic pigs (29). In the 20 pigs who received a coated stent, no thrombotic events were recorded at the time of sacrifice 4 weeks or 12 weeks after implantation. Of the 19 pigs, with a non-coated stent, 7 thrombotic events were recorded ($p<0.01$).
These in vitro and in vivo studies of thromboresistance of the heparin coated stent formed the basis for the imlantation in humans, in the Benestent-II pilot study. In this study, no subacute thrombotic occlusion occurred in any of the patients. In phase I one patient received a bailout stent and in phase II one patient died. Neither event was related to the heparin coating of the stent. In the respective four phases there was a trend to a decreasing incidence of bleeding complications, resulting in a shorter hospitalization time.
Factors other than the heparin-coating may also have contributed to this improved outcome when compared to the Benestent-I study. There may have been better patient selection (larger RD and MLD), better stent implantation technique (more frequent use of on-line QCA- online, larger balloon size and higher post stent dilatation inflation pressures) and achievement of a better stent result (larger RD and MLD post stenting and reduced diameter stenosis). The new antiplatelet treatment (Ticlopidine) may have contributed to improved outcome, when compared to the Benestent-I study results.

It is thus concluded that postponement of heparin treatment, 6, 12 and 36 hrs after sheath removal has not resulted in (sub-)acute occlusions in these patients treated with antivitamin K. A trend towards less bleeding and peripheral vascular complications is observed.
Substitution of heparin and coumadin with the antiplatelet agents, aspirin and ticlopidine, did not result in stent thrombosis and bleeding complications. Heparin coated stents are well tolerated, as no thrombogenic, allergic, toxic or immunologic side effects were encountered. However, the profile of the SDS should be improved, since this was the factor, limiting procedural success.

The absence of (sub)acute occlusion as well as the virtual disappearance of bleeding and peripheral vascular complications in phase IV (ticlopidine and aspirin only), confirm the feasibility of a randomized trial testing the clinical value of this new stent, as well as the innocuous nature of the new post treatment regimen.

Based on the data of the Benestent-II pilot study, the Benestent-II trial has been deigned. In this multicenter randomized study, the hypthesis is tested that the use of a heparin-coated Palmaz Schatz stent in conjunction with acetyl salicylic acid and ticlopidine in patients with stable and classes I and II unstable angina will:
- reduce hospital stay, risk of bleeding and vascular complications resulting in similar rates to that following ballloon angioplasty, without increasing the risk of (sub)acute stent thrombosis;
-further reduce the restenosis rate resulting in a further reduction in the need for repeat revascularization when compared to PTCA.

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SUMMARY

Implantation of metallic coronary stents is a promising strategy to obtain improvement of suboptimal results and for prevention of restenosis after percutaneous transluminal coronary balloon angioplasty (PTCA). However, clinical studies revealed two major problems, associated with this technique. Metallic coronary stents are prone to thrombotic occlusion, which is usually prevented by using complex anticoagulation regimens. Intense anticoagulation after a transarterial coronary intervention in turn is associated with a high risk for access- site related bleeding complications. Both complications may affect the overall applicability of the technique, since they are potentially life threatening and because they are associated with patient discomfort, prolonged hospitalization times and increased costs.
This thesis gives an inventory of our efforts to overcome the problems associated with implantation of Palmaz Schatz coronary stents, in order to optimize clinical outcome of this intervention.

SUMMARY OF FINDINGS

First the results and problems associated with implantation of Palmaz Schatz coronary stents for two major indications are discussed in chapters 2 and 3.
We described our results of Palmaz Schatz stenting for failed PTCA, during very early stent experience (chapter 2.1 and 2.2). In the larger series, procedural success was achieved in 89%. However, 23% of 39 conservatively treated patients sustained subacute stent occlusion and a major bleeding was encountered in 3 patients (8%).

Although Palmaz Schatz stent implantation was associated with a more favorable short and long term outcome compared to balloon angioplasty in selected patients with stable angina and a de novo lesion in native coronary arteries (Benestent-I study; chapter 2.3), the results were partially offset by a 3.5% subacute stent occlusion rate and a 13.5% incidence of major bleeding complications, requiring vascular surgery and/or bloodtransfusions.
In a multivariate analysis performed on patients randomized to stent implantation in the Benestent study (chapter 3.1), risk for subacute stent thrombosis appeared to be a small preprocedural vessel size, prior myocardial infarction and the occurrence of bleeding complications. Female patients were at higher risk for bleeding complications.

In chapter 4, solutions for stent thrombosis and bleeding complications are explored in 5 directions: [a] improvement of stent deployment, [b] improvement of anticoagulation monitoring, [c] improvement of local hemostasis, [d] selection of safer entry sites and [e] decreased thrombogenicity of the stent.

[a] Intravascular ultrasound plays an important role in the proper assessment of stent deployment (chapter 4.1). It was found that 21 of 29 stents (72%) were suboptimally deployed after implantation with the sheath protected stent delivery system. Improvement was achieved by high pressure dilatations with less compliant balloon material. Since we expected that early and long term outcome improves with improved stent deployment, we routinely perform high pressure stent dilatations with adequate sized balloons.

[b] A second prerequisite for a successful outcome was considered to be optimal anticoagulation. Since an optimal level of anticoagulation depends on optimal monitoring, assessments of prothrombin fragment (PTF) F1+2 was recommended by several investigators. Despite convincing reports, we were not able to demonstrate a relation between elevated levels of PTF F1+2 and stent thrombosis in a prospective study (chapter 4.2). Blood sampling and analysis have been performed correctly. The variability of laboratory results may be due to storage techniques. However, in the patients with a bleeding complication, levels were higher, compa-

red to patients without a bleeding, which is not surprising, since formation of thrombin is the natural answer on any bleeding and hemostasis process. Because of this variability in results and since thrombus formation secondary to a bleeding can not be differentiated from thrombus formation due to impending stent thrombosis, we decided not to perform this costly and time-consuming monitoring of PTF F1+2 after Palmaz Schatz stent implantation.

[c] With enthousiasm, a new hemostasis device, a collagen plug (Vasoseal®) was wellcomed in our department, with the expectation that safe and early mobilization of patients under full heparinization would become feasible. Immediate sheath removal followed by stable local hemostasis, would allow the clinician to maintain heparinization on a high level, without interruption of the heparin infusion. In a retrospective study, comparing patients with and without a Vasoseal® after stenting, we were able to demonstrate a better level of heparinization, with less suboptimal APTT- values in patients treated with a Vasoseal®; 7% of 233 APTT samples, versus 20% of 168 samples in patients without a hemostasis device (chapter 4.3). Early and late puncturesite bleeding complications, however, could not be prevented, limiting the applicability of this costly device.

[d] Another possible means to obtain improved local hemostasis is the use of smaller guiding catheters and introducer sheaths, which became possible since miniaturized angioplasty material became compatible with 6 French (F) guiding catheters.
Instead of using these catheters by the traditional transfemoral technique, we explored the feasibilty of transradial coronary angioplasty, since several advantages of this approach are evident: the superficial course allows safe and effective hemostasis, the absence of major nerves and veins near the radial artery excludes damage to these structures, and collateral blood supply from the ulnar artery prevents the hand from becoming ischemic if the radial artery occludes.

Maintenance of the possibility to treat suboptimal results such as occlusive coronary dissections with autoperfusion balloons or coronary stents, may currently be considered as a prerequisite for any new PTCA- technique. New low profile perfusion balloon catheters proved to be compatible with 6F guiding catheters (inner diameter 0.060 inch) for primary use (chapter 4.4.1), although friction was noticed during introduction and removal of the balloon catheter from the guiding catheter. Re-introduction after removal was impossible in 3 of 5 patients. Applicability of perfusion balloons or coronary stents via 6F guiding catheters for suboptimal PTCA- results is reported in 13 patients (chapter 4.4.2). Thus 6F transradial coronary angioplasty can be performed, without losing the possibility to optimize poor immediate PTCA results with the two most commonly applied techniques.

In order to study the feasibility of transradial balloon angioplasty, we performed an open prospective study in 100 patients (chapter 4.5.1.). Coronary catheterization via the radial artery was successful in 94 patients. Of these patients a procedural success was achieved in 92 patients (98%). Radial artery occlusion occured in 10% of patients. Spontaneous recanalisation was evident in 5%. No patient had signs of ischemia of the hand and forearm and no major bleeding complications were encountered.
Encouraged by these promising results we designed a randomized study, the ACCESS- study, to establish the mutual relation of access-failure rates and vascular complications of PTCA with 6F guiding catheters via the percutaneous femoral, brachial or radial artery.
The interim analysis (450 patients) is described in chapter 4.5.2.
During this first part of the study, coronary cannulation was successfully achieved in 92.1% of patients, randomized to the transradial artery approach, versus 96.6% (p=0.03) and 100% (p=0.001) in the patients who underwent PTCA via the brachial and femoral artery. Failed radial artery puncture was the main reason for inability to cannulate the coronary artery.

Procedural PTCA succesrates were comparable in the three groups. After PTCA via the percutaneous brachial route, bleeding complications were more frequently encountered; 4.1%, versus 0% (p=0.03) in the radial group and 1.3% (p=ns) in the femoral group.

The transradial approach is theoretically an ideal technique for coronary stenting since both stent thrombosis and bleeding can be reduced by giving full anticoagulation in an ambulant patient, treated via a low risk entry site. By manual crimping of a bare Palmaz Schatz stent on low-profile balloon catheters, we were able to deliver these stents via the radial artery. The technique of transradial artery stenting is described in a case report (chapter 4.6.1.) and results of this technique are described in 20 patients (chapter 4.6.2) and in 100 patients (chapter 4.6.3). In this final series, we were able to demonstrate high procedural (96%) and clinical success rates (93%). Stent thrombosis was encountered in 1 patient (1%) and another patient had a radial artery bleeding requiring vascular surgery (1%).

Because of the important role of intravascular ultrasound during coronary stenting, it was necessary to demonstrate the feasibility of transradial ultrasound controlled stent implantation via 6F guiding catheters. Feasibility of transradial ultrasound controlled stenting with miniaturized vascular ultrasound transducers, is demostrated in 8 patients (12 stents) (chapter 4.6.4). We found improved stent expansion after high pressure dilatations with balloons of intermediate compliance, compared to the results after delivery with equally sized compliant balloons at 10-12 atmospheres.

Transradial implantation of bare stents has the potential for significant cost savings, when compared to the traditional transfemoral stent technique, using 8F guiding catheters and sheath protected stent delivery systems. Savings are potentially achieved by a reduction of costs associated with use of material (less balloon catheters), with diagnosis and treatment of bleeding complications and by a shorter hospitalization time. We compared the costs of these items in 35 patients after elective single stent implantation via the radial artery to those of 25 patients, participating in the Benestent study in our clinic, who received a stent via the femoral artery (chapter 4.6.5). Overall, the mean cost per patient in the first group was 67% of costs in the second group.

The transradial approach for stenting allows the patient to be mobilized immediately after the procedure. Together with the high success rate and the low complication rate, hospital stay was relatively short, compared to historical series. Patients on a preprocedural adequate level of oral anticoagulation could be discharged the day following stent implantation (n=22 in the series of 100 patients), if no complications were observed. Since acute stent thrombosis is an extremely rare event, there is no argument to keep patients inhospital, if adequate local hemostasis is obtained in an ambulant patient on a therapeutic level of anticoagulation. We conducted a pilot study (20 patients) to the feasibility of transradial outpatient coronary stenting (chapter 4.6.6).
Since no complications were associated with this outpatient strategy, the 95% confidence interval for an event-free outpatient procedure runs from 0-16.8%. A feasibility study in 100 patients is presently conducted in our department.

Thus the transradial approach can be considered as a major breakthrough in the optimalization of coronary stenting, since this approach is effective, safe and is associated with increased patient comfort (early mobilization) and cost effectiveness.

Another means to reduce the risk for stent thrombosis and local bleeding complications is the use of non-thrombogenic, heparin coated coronary stents, which allows withdrawal or at least a reduction of anticoagulants. Results of a pilot study on the use of heparin coated stents in

patients with stable angina and a de novo lesion in a native coronary artery (Benestent II-pilot study; phase 1,2,3 and 4) are described in chapter 4.7.
In 4 patient groups, heparinization after sheath removal was gradually delayed to 36 hours. In the fourth group, no heparin was administered after the procedure and the patients were treated with antiplatelet drugs instead of antivitamin K. The heparin-coated stent was well tolerated. No stent thrombosis was encountered. A trend towards less access- related bleeding complications was observed. This study confirms the feasibility of a randomized trial testing this new stent.

CLINICAL CONSEQUENCES

What do all these findings mean for day-to-day care of patients, selected for coronary stent implantation?

Elective as well as emergent coronary stenting, for reduction of restenosis and for improvement of suboptimal PTCA results, respectively, should be finalized by high-pressure dilatations of the freshly implanted stent, to a diameter, at least corresponding to the reference diameter of the stented segment, in order to reduce the risk for stent- occlusion. An optimal stent result provides a good safe-guard against thrombotic stent- occlusion. Variability of results of prothrombin fragment F1+2- monitoring in the week following stent implantation, limits the value of this costly and time consuming tool, in the prevention of stent- thrombosis.

The main hazard of coronary stenting through 8F guiding catheters via the femoral artery under full anticoagulation is a local bleeding complication, which can not be prevented by percutaneous insertion of collagen plugs.

One effective strategy to prevent bleeding complications is the transradial artery stent technique. This approach is technically more delicate and difficult than the transfemoral technique, since the radial artery is smaller and the guiding catheters are preshaped for the femoral approach. Despite these limitations, we have shown that the transradial approach can safely and effectively be applied in patients undergoing coronary balloon angioplasty and coronary stenting, without losing the possibilty to apply bailout techniques and intravascular ultrasound. The dramatic reduction of bleeding complications is evident, resulting in reduction of costs, since less diagnostic and therapeutic procedures are required for treatment of these complications. No ischemic damage to the hand or forearm was observed. The combination of effective and safe hemostasis and reliable stent results makes coronary stenting on an outpatient basis possible, which will contribute to further cost- reduction.

Another promising technique to reduce the risks for stent thrombosis as well as bleeding complications, is the use of non-thrombogenic heparin coated stents. These stents allow patients to be treated with a simplified anticoagulation regimen. Its effect on restenosis and cost savings will be explored in a randomized multicenter study.

SAMENVATTING

Implantatie van roestvrij stalen coronaire stents is een veelbelovende techniek ter verbetering van suboptimale resultaten na percutane transluminale coronaire ballon angioplastiek (PTCA) en ter preventie van restenose na PTCA.
Er zijn echter twee belangrijke beperkingen aan deze techniek verbonden. In de metalen stents kan thrombose optreden. Om thrombotische occlusie van de stent te voorkomen worden de patiënten na stent implantatie veelal nabehandeld met een complexe combinatie van stollingsremmers. Intensieve ontstolling na een arteriële catheterisatie procedure, kan gepaard gaan met ernstige bloedingcomplicaties.
Beide, potentieel levensbedreigende, complicaties beperken de algemene toepasbaarheid van de stent techniek. Ook gaan deze complicaties gaan gepaard met ongemak voor de patiënt, langdurig ziekenhuis verblijf en met hoge kosten.
Dit proefschrift geeft een overzicht van onze inspanning om het klinische resultaat van coronaire Palmaz Schatz stent implantatie te optimaliseren.

SAMENVATTING VAN DE BEVINDINGEN

Eerst worden de resultaten en complicaties besproken van stent implantatie voor de twee belangrijkste indicaties in onze kliniek.

De eerste ervaring met de Palmaz Schatz stent werd in ons centrum opgedaan gedurende de behandeling van suboptimale PTCA resultaten als alternatief voor acute coronaire bypass chirurgie (hoofdstuk 2.1 en 2.2). Procedureel succes van stent implantatie werd bereikt in 89% . Echter, 23% van de 39 niet-chirurgisch behandelde patiënten, ontwikkelde stent thrombose en belangrijke bloedingscomplicaties werden gezien bij 3 patiënten (8%).

De klinische en angiografische resultaten na stent implantatie waren beter dan na conventionele PTCA bij geselecteerde patiënten met stabiele angina pectoris en een primaire laesie in een kransslagader (Benestent-I studie; hoofdstuk 2.3). Echter, de voordelen werden ten dele teniet gedaan door stent thrombose (3.5%) en door bloedings- complicaties, waarvoor een chirurgische ingreep of het toedienen van bloedtransfusies noodzakelijk was (13.5%).
Multivariate analyse van de stent populatie (hoofdstuk 3.1) leerde dat de kans op stent thrombose groter is naarmate de preprocedurele kransslagader diameter kleiner is, als de patiënt vroeger een hartinfarct heeft doorgemaakt en als er na de procedure een bloeding optreedt. Vrouwen hebben een grotere kans op een bloedingscomplicatie.

Oplossingen voor stent thrombose en bloedingscomplicaties werden gezocht in verbetering [a] van de implantatie techniek, [b] van de controle op ontstolling, [c] van lokale hemostase en [d] in de selectie van een veiliger punctieplaats en [e] in de vermindering van de thrombogeniciteit van de stent (hoofdstuk 4).

[a] De toepassing van intravasculaire echografie speelt een belangrijke rol in de beoordeling van de mate en kwaliteit van stent expansie in de kransslagader (hoofdstuk 4.1).
Wij constateerden met behulp van deze techniek dat 21 van de 29 stents (72%), na aflevering met het "Stent Delivery System" onvoldoende ontplooid waren. Verbetering werd verkregen na hoge inflatiedrukken met grotere ballonnen van geringere compliantie. Deze bevindingen zijn in overeenstemming met observaties van andere onderzoekers en tegenwoordig wordt routinematig het acute stent resultaat geoptimaliseerd middels nadilataties met hoge inflatiedrukken.

[b] Optimale ontstolling vereist optimale monitoring hiervan. Door diverse onderzoekers werden Prothrombine fragment F1+2 bepalingen aanbevolen. Wij konden echter geen relatie con-

stateren tussen verhoogde prothrombine fragment F1+2- waarden en stent thrombose in een prospectieve studie (hoofdstuk 4.2). Bloedafname en -bepaling waren correct uitgevoerd. De sterke variabiliteit van de uitkomsten kan eventueel samenhangen met het feit dat de plasmamonsters eerst waren ingevroren, totdat bepaling plaatsvond.
Het bleek echter dat bij patiënten, die ook een bloeding hadden doorgemaakt, hogere waarden werden gevonden. Dit is verklaarbaar uit het feit dat de vorming van thrombine een natuurlijk antwoord is op iedere bloeding. Vanwege de variabiliteit van de uitkomsten en vanwege het feit dat thrombusvorming, secundair aan een bloeding niet kan worden gedifferentieerd van thrombusvorming bij dreigende stentocclusie, hebben wij besloten prothrombine fragment F1+2- monitoring niet als routine na stent implantatie in te voeren.

[c] Met enthousiasme werd de collageen-plug (Vasoseal) geïntroduceerd op onze afdeling. Wij koesterden de verwachting dat deze noviteit veilige en vroege mobilisatie van de geheparíniseerde patiënt zou toelaten. Tevens zou het mogelijk zijn op hoog niveau te kunnen heparíniseren, onmiddellijk nadat hemostase middels de Vasoseal zou zijn verkregen. In een retrospectieve studie, waarbij patiënten met en zonder Vasoseal na stent implantatie met elkaar werden vergeleken, bleek inderdaad dat er sprake was van een optimaler heparinisatie. Er werden minder subtherapeutische APTTs gevonden in de patiënten met een Vasoseal; 7% van 233 APTTs versus 20% van 168 APTTs (hoofdstuk 4.3). Lokale bloedingen konden echter niet worden vermeden, hetgeen de toepasbaarheid van deze, ook kostbare, plug beperkt.

[d] Een andere methode om tot verbeterde hemostase te komen, is het gebruik van de kleinere, 6 French (F), geleidecatheters. Wij hebben onderzoek gedaan naar de haalbaarheid van de arteria radialis, als port d'entrée. Er zijn immers een aantal theoretische voordelen aan deze methode verbonden: de oppervlakkige ligging van de arteria radialis maakt dit vat gemakkelijk afdrukbaar, er lopen geen belangrijke aders en zenuwen naast de polsslagader en de collaterale verbindingen met de arteria ulnaris beschermen de hand tegen ischemie in geval van een postoperatieve arteria radialis afsluiting.

Wij hebben als voorwaarde voor de transradiale PTCA techniek met 6F geleidecatheters gesteld dat de patiënt met autoperfusieballonnen en met stents behandeld moeten kunnen worden, indien de PTCA een onvoldoende resultaat geeft. In hoofdstuk 4.4.1. worden onze ervaringen beschreven met nieuwe perfusieballonnen, opgevoerd door 6F geleidecatheters. Alhoewel er wel enige frictie voelbaar was, konden deze ballonnen wel ter plaatse van de stenose worden gebracht. Re-introductie, nadat de ballon uit de catheter was teruggetrokken, faalde bij 3 van de 5 patiënten. De toepasbaarheid van perfusieballonnen en stents ter verbetering van suboptimale PTCA resultaten wordt beschreven bij 13 patiënten (hoofdstuk 4.4.2.). Wij hebben hiermee dus aangetoond dat PTCA door 6F geleidecatheters de 2 cathetertechnieken, om tot verbetering van PTCA resultaten te komen, niet uitsluit.

Vervolgens hebben wij een prospectieve studie verricht naar de resultaten van transradiale PTCA in een serie van 100 patiënten (hoofdstuk 4.5.1.). Bij 94 patiënten kon de kransslagader worden gecannuleerd. De procedure verliep succesvol bij 98%. Bij 10 patiënten bleek de arteria radialis te zijn afgesloten voor ontslag uit het ziekenhuis, doch spontane rekanalisatie vond plaats bij 5 patiënten. Belangrijke bloedingscomplicaties of ischemie van de hand zijn niet opgetreden.
Gestimuleerd door deze resultaten, hebben wij een gerandomiseerde studie opgezet (de ACCESS- studie) naar cannulatie- en catheterisatiesucces en bloedingscomplicaties, bij percutane transradiale, -brachiale en -femorale ballon coronaire angioplastiek met 6F geleidecatheters. Een interim-analyse werd verricht na inclusie van 450 patiënten (hoofdstuk 4.5.2.). Bij 92.1% van de patiënten uit de radialis- groep kon de kransslagader worden gecannuleerd, tegen 96.6% (p=0.03) an 100% (p=0.001) van de patiënten uit respectievelijk de brachialis-

en de femoralis- groep. Procedureel PTCA succes was vergelijkbaar in de 3 groepen. Meer bloedingscomplicaties traden op na PTCA via de arteria brachialis (4.1%), versus 0% na transradiale PTCA (p=0.03) en 1.3% na transfemorale PTCA (p=NS). De ACCESS- studie wordt gecontinueerd totdat 900 patiënten zijn geïncludeerd.

De transradiale benadering is theoretisch ideaal voor patiënten, die een stent geïmplanteerd krijgen, omdat stent thrombose kan worden voorkomen, door optimaal te ontstollen, zonder een belangrijk bloedingsrisico. De combinatie van manueel gemonteerde stents op balloncatheters met een laag profiel, bleek goed compatibel met 6F geleidecatheters. De techniek van transradiale coronaire Palmaz Schatz stent implantatie wordt beschreven in een casuïstische mededeling (hoofdstuk 4.6.1.) en de resultaten worden beschreven bij 20 patiënten (hoofdstuk 4.6.2.) en bij 100 patiënten (hoofdstuk 4.6.3.). In deze laatste serie vermeldden wij een 96% procedureel succes en 93% klinisch succes. Stent thrombose werd bij 1 patiënt (1%) geconstateerd en 1 patiënt (1%) had een belangrijke lokale bloeding.

Gezien de belangrijke rol van intravasculaire echografie gedurende stentimplantaties, hebben wij een haalbaarheidsstudie gedaan naar transradiale ultrasoon geleide coronaire Palmaz Schatz stent implantatie bij 8 patiënten {12 stents} (hoofdstuk 4.6.4.).
Wij constateerden betere stent expansie na hoge druk- inflaties met semi-compliant ballonnen, vergeleken met de expansie na aflevering met 10-12 atmosfeer met compliant ballonmateriaal.

Transradiale stent- implantatie is goedkoper dan de traditionele transfemorale techniek, met 8F geleidecatheters en het Stent Delivery System. Wij vergeleken de kosten tussen 25 patiënten, die op deze wijze gestent zijn (Benestent- populatie OLVG) en 35 patiënten na electieve stent implantatie via de polsslagader. Kosten werden bespaard op materiaal verbruik, diagnostiek en behandeling van bloedingscomplicaties en op ziekenhuis- opnameduur. De totale kosten na een transradiale stentimplantatie bedroegen 67% van de kosten van de traditionele methode (hoofdstuk 4.6.5.).

Na een transradiale stent- behandeling is de patiënt onmiddellijk mobiel. Daar hemostase effectief kan worden verkregen en daar de kans op stent occlusie, na een optimaal acuut resultaat, gering is, resteren er weinig argumenten om goed ontstolde patiënten klinisch te houden, na een succesvolle ingreep.
Bij 20 patiënten hebben wij een pilot-studie verricht naar de mogelijkheid om op poliklinische basis Palmaz Schatz coronaire stents te implanteren (hoofdstuk 4.6.6.).
Bij geen van deze zorgvuldig geselecteerde patiënten hebben zich complicaties voorgedaan, gerelateerd aan het poliklinisch protocol (betrouwbaarheidsinterval voor een ongecompliceerd beloop; 0-16.8%). Thans wordt de studie naar een grotere groep patiënten uitgebreid.

Dus de transradiale benadering voor Palmaz Schatz coronaire stent implantatie kan als een doorbraak worden beschouwd, daar deze techniek effectief en veilig is. De patiënt- en budget vriendelijkheid zijn belangrijke additionele voordelen.

Een andere methode om zowel de kans op stent thrombose als op bloedingscomplicaties te verkleinen, is het gebruik van niet-thrombogene, heparine- gecoate, stents in combinatie met een sterk vereenvoudigd ontstollingsbeleid. Resultaten van de pilot- studie, betreffende heparine-gecoate stents bij patiënten met stabiele angina pectoris en een de novo stenose in een kransslagader (Benestent-II pilot study; fase 1,2,3,en 4) worden beschreven in hoofdstuk 4.7. In de eerste 3 fasen werd de heparinisatie na verwijderen van de sheath, uitgesteld van 6 naar 12 naar 36 uur. In de 4e fase werd geen heparine post-procedureel meer toegediend en werd antivitamine K vervangen door plaatjesaggregatieremmers. Er werd geen stent thrombose

waargenomen en er was een afname van het aantal lokale bloedingscomplicaties te constateren. Deze studie bevestigt de haalbaarheid van een gerandomiseerde studie, waarbij resultaten van PTCA zullen worden vergeleken met resultaten na implantatie met deze stent.

KLINISCHE BETEKENIS
Wat betekent dit allemaal voor de dagelijkse praktijk?

Electief stenten ter preventie van restenose en spoedimplantaties ter verbetering van suboptimale PTCA resultaten zijn 2 (klinisch) geaccepteerde indicaties voor Palmaz Schatz coronaire stents. Gedurende de vroege ervaring werden stentimplantaties te vaak gecompliceerd door thrombotische stentocclusie en door lokale bloedingen.

Een optimaal acuut stentresultaat is waarschijnlijk de beste beveiliging tegen het optreden van stent thrombose en plaatst het ontstollingsbeleid in een ander perspectief.
De stents dienen te worden nagedilateerd met minder compliant ballon materiaal en met hoge inflatiedrukken. Gestreefd moet worden naar een optimale verhouding tussen stent diameter en diameter van de kransslagader (tenminste 1:1).

De variabiliteit van prothrombine F1+2- bepalingen in de week na stent implantatie, beperkt de waarde van deze kostbare en tijdrovende techniek en is als routine niet aan te bevelen.

Het subcutaan plaatsen van collageen-pluggen ter preventie van liesbloedingen na een 8F procedure onder volledige ontstolling, vindt geen grote navolging. In onze ervaring heeft dat ondermeer te maken met het feit dat bloedingscomplicaties niet kunnen worden voorkomen en dat deze zelfs dagen na de insertie kunnen optreden.

Een effectieve methode om bloedingscomplicaties te voorkomen is de transradiale stent techniek. Deze benadering is technisch moeilijker dan de transfemorale techniek, daar de arteria radialis kleiner is en daar de meeste geleidecatheters niet op deze benadering zijn ontworpen. Deze beperkingen ten spijt, hebben wij aangetoond dat de radialis techniek effectief en veilig kan worden toegepast voor PTCA en Palmaz Schatz coronaire stentimplantaties. Transradiale coronair angioplastiek sluit de toepassing van "bail-out" technieken en intravasculaire echografie niet uit.
De belangrijke reductie in bloedingscomplicaties heeft ook een kostenreductie tot gevolg, daar minder diagnostische en therapeutische verrichtingen noodzakelijk worden en daar de opnameduur kan worden bekort. Ischemische complicaties aan de hand, bij patiënten met collaterale verbindingen met de artria ulnaris, zijn niet waargenomen.
De combinatie van effectieve en veilige hemostase met een betrouwbaar stentresultaat, maakt deze behandeling op poliklinische basis mogelijk, hetgeen zal bijdragen tot een verdere kostenreductie.

Een andere veelbelovende techniek ter bestrijding van stent thrombose en locale bloedingscomplicaties is het gebruik van heparine-gecoate stents. Deze stents maken het mogelijk de complexe ontstollingsregimes te vervangen door veiliger plaatjesaggregatieremmende regimes. Het effect op restenose en kosten-reductie wordt in een gerandomiseerd multicentrisch onderzoek geëvalueerd.

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