Primary PCI and Treatment of Reperfusion Injury in Acute Myocardial Infarction

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PRIMARY PCI AND TREATMENT OF REPERFUSION INJURY IN ACUTE MYOCARDIAL INFARCTION

Primaire PCI en behandeling van reperfusieschade
in het acute myocardinfarct

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Ter herinnering aan papa en Gitta

Voor mama en Vanessa

CONTENTS

CHAPTER 1

GENERAL INTRODUCTION & OUTLINE OF THESIS

Acute myocardial infarction (AMI) is responsible for the majority of (sudden) deaths and significant morbidity, thereby causing a major burden on health care. The prognosis of patients after an AMI is mainly determined by the size of the infarct, which is dependent of the area at risk (determined by localization of coronary occlusion), the duration of ischaemia, the severity of ischaemia (which is dependent on the degree of collateral flow and residual antegrade flow), and the mode of reperfusion.[1] Any (ST-segment elevation) AMI should be reperfused as fast as possible ("time is muscle"), with primary percutaneous coronary intervention currently being considered as the optimal approach to the reperfusion therapy of myocardial infarction with ST-segment elevation.[2] New insights into the pathophysiology, diagnosis and treatment strategies are generated striving to further improve treatment of patients with an AMI.

This thesis describes several aspects of acute myocardial infarction. Specifically it aims to:

1) Obtain better insight in the *pathophysiology* of by investigating atherosclerotic plaque formation.
2) Evaluate the accuracy of the electrocardiogram in the *diagnosis* of AMI.
3) Limit the complications of percutaneous coronary intervention in the *treatment* of AMI by use of the transradial artery approach and to study the efficacy and safety of drug-eluting stents in patients with AMI.
4) Reduce the *sequelae* of AMI by limiting reperfusion injury (i.e. revascularization by primary percutaneous coronary intervention or thrombolysis) itself; and finally, review clinical trials on reperfusion injury inhibitory strategies in patients with AMI.

PATHOPHYSIOLOGY OF ACUTE MYOCARDIAL INFARCTION: PLAQUE STABILITY

An AMI occurs when a coronary artery supplying the heart becomes occluded. This occlusion is typically caused by rupture of destabilized atherosclerotic plaques inside the arterial wall, triggering the formation of thrombus,[3-7] which can occlude the artery, causing cardiac ischaemia. Prolonged ischaemia can lead to infarction, reducing the power of the heart to pump oxygenated blood around the body, and potentially leading to heart failure and death. Improved insight in the pathophysiology of AMI may generate potential treatment strategies, therefore it is of importance to study the factors responsible for plaque destabilisation. Destabilisation of an atherosclerotic plaque is thought to be mainly caused by a dynamic inflammatory process[8-10] and it has been suggested that the amount of wall shear stress may be partly responsible for the destabilisation of plaque content.[11-14] *Consequently, the influence of the direction of flow or shear stress on the distribution of cells in an atherosclerotic plaque will be studied in Chapter 2.*

DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION: THE ELECTROCARDIOGRAM

The typical presentation of an AMI is a patient presenting with chest pain, discomfort and/or dyspnea, with or without radiation to the jaws and arms and/or vegetative symptoms (nausea, vomiting, anxiety) that lasts for at least twenty minutes. The clinical diagnosis is based on these complaints in combination with electrocardiographic changes. More than 100 years after Einthoven's first publication on the electrocardiogram,[15] the electrocardiogram has become indispensable for rapid diagnosis and management of patients with a wide variety of cardiac diseases, including AMI.[16] The electrocardiogram is easily available, non-invasive, inexpensive and crucial in the diagnosis of AMI. The main criteria for ST-segment elevation myocardial infarction on the electrocardiogram are new or presumed new ST-segment elevations at the J point in two or more contiguous leads with the cut-off points ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.[17] The electrocardiogram not only indicates the presence of AMI, but can also be used for estimation of the size of the area at risk[18] and localization of jeopardized area. It has been claimed that localization of the infarct related coronary artery and infarct related (culprit) coronary segment can be predicted based on electrical vector theory of the ST-segment deviation (elevation or depression) from the isoelectric line in the 12-lead electrocardiogram.[19,20] *Several electrocardiographic criteria to diagnose the site of origin of occlusion in the coronary artery have been published,19,20 that are mainly based on (electrical vector) theories or non-blinded studies. Consequently, the validity and accuracy of the criteria in clinical practice are evaluated in Chapter 3.*

TREATMENT OF ACUTE MYOCARDIAL INFARCTION: NOVEL TREATMENT STRATEGIES IN PRIMARY PCI

Limitation of myocardial infarct size is critical to improve immediate and long-term outcome and to reduce the incidence and prevalence of heart failure. The principal therapy to limit infarct size in patients with an AMI is reperfusion by revascularization with a mechanical (percutaneous coronary intervention) or pharmacological intervention (thrombolysis).[2] Currently, percutaneous coronary intervention with intracoronary stent implantation is considered to be superior to balloon angioplasty alone or thrombolysis in patients suffering from an acute ST-segment elevation myocardial infarction.[21-23] In order to achieve a further improvement of outcome after a percutaneous coronary intervention with stent implantation, it is mandatory to further reduce complications, hospital stay and the need for repeat revascularization. These issues will be evaluated in Chapters 4-7.

Primary Percutaneous Coronary Intervention Using the Transradial Approach

In addition to percutaneous coronary intervention, recent studies have documented further improvement in outcomes after primary percutaneous coronary intervention when a glycoprotein IIb/IIIa receptor blocker (abciximab) is added to the regime.[24-27] A glycoprotein IIb/IIIa receptor blocker may improve microvascular flow by preventing thrombus formation and embolization triggered by damage of the endothelium and stent material.[25,28] Although not yet proven to be as beneficial as abciximab when administered supplementary to primary percutaneous coronary intervention, the cheaper glycoprotein IIb/IIIa receptor blocker tirofiban is also widely used. Despite its beneficial effects, it is well recognized that, predominantly entry-site related bleeding complications, are a frequent companion of glycoprotein IIb/IIIa blocker treatment (12% in the ADMIRAL-trial)[25] resulting in additional morbidity and prolonged hopitalization.[29-31] By using the transradial approach for arterial access this additional morbidity by local bleeding can be minimized.[32,33] Furthermore, it has been suggested that patients with an AMI could be discharged early (3-4 days) when treated by a primary percutaneous coronary intervention.[34] Reduction of hospital stay is not only generally well appreciated by patients, it also has advantages for the hospital and cardiology departments, since it allows effective use of hospital capacity and resources.[34] The combination of the above mentioned potential beneficial strategies may improve the treatment regimen for patients with an AMI. *Consequently, the feasibility to discharge patients shortly (3-4 days) after a primary percutaneous coronary intervention for AMI, in combination with the use of the transradial approach and the glycoprotein IIb/IIIa receptor blocker tirofiban is investigated in Chapter 4.*

Drug-Eluting Stents in Acute Myocardial Infarction

Implantation of intracoronary stents has been shown to limit the need for repeat revascularization in patients that underwent a primary percutaneous coronary intervention for AMI, compared to balloon angioplasty alone.[21-23] However, restenosis may still develop after stent implantation,[27,35] resulting in repeat revascularization rates up to 20% after bare metal stent implantation after primary percutaneous coronary intervention.[36,37] Repeat revascularization exposes the patients to additional risk from repeat catheterization and revascularisation by percutaneous coronary intervention or coronary artery bypass grafting, resulting in an increased burden of death, recurrent myocardial infarction, and left ventricular dysfunction.[38-40] Drug-eluting stents reduce target-vessel revascularization for restenosis as compared with bare-metal stents in a variety of clinical pictures.[41,42] Currently, there are several drug-eluting stents commercially available, the first two on the market were the sirolimus-eluting stent and the paclitaxel-eluting stent. Retrospective studies and one small randomized trial have suggested that the use of drug-eluting stents is also beneficial in the setting of primary percutaneous coronary intervention,[43-46] warranting a larger randomized trial in patients with AMI. *Consequently, the efficacy of paclitaxel-eluting stents was studied in the Paclitaxel-eluting*

Stent versus Conventional Stent in Myocardial Infarction with ST-segment Elevation (PASSION) trial, which is described in Chapter 5.

Recently, concern has arisen regarding serious adverse events caused by stent thrombosis late after drug-eluting stent implantation.[47-49] There is a growing concern that delayed endothelialization,[50,51] late malapposition,[52] impaired endothelial function[53] and reduced neointimal response[54] after drug-eluting stent implantation may lead to late (> 30 days) and very late (> 1 year) stent thrombosis. Stent thrombosis is a potentially hazardous adverse event, which may lead to recurrent myocardial infarction or death. Additionally, it has been suggested that the occurrence of late stent thrombosis may be associated with the cessation of clopidogrel after 6-12 months after stent implantation. It was recently stated by the Food & Drug Administration panel (Nov 2006) that off-label use of drug-eluting stents (i.e. including ST-segment elevation myocardial infarction) is associated with increased risks of both early and late stent thrombosis. However, the event rates late after primary percutaneous coronary intervention with drug-eluting stents are unknown. *To address this issue, in Chapter 6 we evaluated the safety of paclitaxel-eluting stents compared to bare-metal stents in the setting of primary percutaneous coronary intervention, in terms of the rate of serious adverse cardiac events, especially in relation to the incidence of stent thrombosis at two years follow-up. Furthermore, in Chapter 7 the effects of drug-eluting stents in AMI were analyzed using meta-analysis of 8 randomized trials, including the PASSION trial, with a total study population of 2.786 patients with a clinical follow-up of 18-24 months .*

SEQUELAE OF ACUTE MYOCARDIAL INFARCTION: REPERFUSION INJURY

Besides reperfusion and conventional anti-platelet therapy, further infarct size limitation may be obtained by adjunctive pharmacological treatment. The importance of immediate reperfusion is not surprising as the primary insult is a decrease in oxygen supply resulting in a decrease of free energy from ATP-hydrolysis beyond a critical level required for maintaining cell processes such as ion channel function. However, despite its clear benefit, reperfusion itself has been proposed to cause irreversible myocardial damage, termed "reperfusion injury", beyond that caused by the preceding period of ischaemia. This implies that optimization of reperfusion therapy by blunting this reperfusion injury could further limit infarct size.

The mechanism of reperfusion injury remains incompletely understood, but may include (*i*) cytosolic and mitochondrial Ca^{2+}-overload, (*ii*) release of reactive oxygen species, (*iii*) an acute inflammatory response, and (*iv*) shift in substrate use.[55-61] These pathways have been the therapeutic targets in experimental and clinical studies. Direct evidence for the existence of reperfusion injury stems from animal studies in which pharmacological agents administered just prior to reperfusion limited final infarct size.[56,62-66] Pre-clinical studies, although sometimes equivocal, spurred a large number of clinical trials. *Chapters 8 and 9 describe two randomized*

clinical trials which evaluated the efficacy of two novel reperfusion inhibitory agents (ITF-1697 in the Protect Against Reperfusion Injury with ITF-1697 in Acute Myocardial Infarction [PARI-MI] and caldaret in the Caldaret [MCC-135] in Patients Undergoing Primary Percutaneous Coronary Intervention for ST-segment Elevation Myocardial Infarction [CASTEMI] trial). ITF-1697 has been shown to exert anti-inflammatory actions by preventing polymorphonuclear neutrophil adhesion and extravasation, preservation of vascular endothelial phenotype and vascular permeability, thereby reducing reperfusion injury (unpublished data on file at Italfarmaco). The intracellular calcium overload induced by ischaemia and reperfusion, another pathway of reperfusion injury, was targeted with the use of caldaret. Caldaret has been shown to enhance uptake and inhibit leakage of calcium from the sarcoplasmic reticulum.[67,68]

In the era of reperfusion therapy more than 35 large clinical trials have been conducted to evaluate the efficacy of several reperfusion injury inhibitory strategies. None of these strategies have indisputable been shown to exert beneficial effects in patients with AMI. *Consequently, in Chapter 10 clinical studies on reperfusion injury inhibitory strategies will be reviewed, with a special emphasis on potential factors that could account for the discrepancies between the oftentimes encouraging results from animal studies and the overall disappointing results from clinical studies. And what can we do to improve the likelihood of success for future studies?*

Finally, in Chapter 11 the results presented in this thesis will be summarized and the impact discussed, with a special emphasis on future research directions.

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CHAPTER 2

THE DISTRIBUTION OF INFLAMMATORY CELLS IN ATHEROSCLEROTIC PLAQUES RELATES TO THE DIRECTION OF FLOW

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ABSTRACT

Background The distribution of macrophages and smooth muscle cells (SMCs) within atherosclerotic plaques is highly variable. This is clinically relevant because these cell types have opposite effects on the stability of atherosclerotic plaques. The present study was designed to investigate whether local variations in arterial flow over the plaque surface could relate to differences in the distribution of SMCs and macrophages in plaques.

Methods and Results Thirty-three entire carotid plaques were collected at autopsy and marked at their proximal (in relation to the direction of the blood flow) ends, and the cell composition of upstream parts (where high flow and high shear prevail) was compared with that of downstream parts (low flow and low shear stress). Seventy percent of plaques showed more SMCs in their downstream part, and 67% of plaques contained more macrophages in the upstream part. Immunostained macrophage areas were larger in upstream parts (P=0.011). Immunostained SMC areas were larger in downstream parts (P=0.031). Rupture sites of 6 of 9 ruptured plaques were in the upstream part.

Conclusions Significant differences in cell composition between upstream and downstream parts of plaques indicate a role for arterial flow in the distribution of different cell types. The low-flow/low-shear downstream areas of plaques contain significantly more SMCs, which could provide the background for slowly progressive growth at distal ends of plaques. The significantly high number of macrophages in the upstream areas suggests a relationship between high flow/high shear and plaque instability.

INTRODUCTION

Atherosclerotic plaques show marked variability with respect to the distribution of inflammatory cells, not only from one lesion to the other but also within one and the same plaque.[1-3] This phenomenon is significant because plaque inflammation is widely considered to play a role in plaque destabilization and, eventually, plaque erosion and rupture.[1,4-8] By the same token, plaques dominated by smooth muscle cells (SMCs) are considered stable. Indeed, coronary atherectomy specimens obtained from patients with chronic stable angina contain SMCs as the dominant cellular component, but in those obtained from patients with unstable angina or acute myocardial infarction, inflammation prevails.[4,9,10]

In view of these considerations, it is important to know which mechanisms could be responsible for these major variations in the cellular composition of atherosclerotic plaques. Hemodynamic factors, such as shear stress, are considered to play a role in plaque growth,[11,12] but thus far the effect of these factors on the cellular composition of atherosclerotic plaques has not been studied. This may well be an interesting enterprise, because the geometry of a bulging plaque dictates differences in the impact of blood flow in relation to the direction

of flow. In fact, the luminal endothelial lining on the upstream (proximal) sites of a plaque is under high shear stress, whereas at downstream (distal) sites, low shear stress prevails.[13,14] We speculated that these differences may also have implications for local variation in the cellular composition of plaques.

To verify this hypothesis, we investigated the relationship between blood flow direction and the cellular composition of carotid plaques by quantitatively comparing SMC and macrophage contents of the upstream shoulder part of plaques with those of the downstream shoulder parts. The common carotid artery with its bifurcation site was chosen, because previous studies by Zarins et al[12] and Ku et al[15] have shown that these arterial sites may serve as a good model to investigate the relationship between fluid dynamics and atherosclerosis and also because the carotid bifurcation is a predilection site for plaque formation.

METHODS

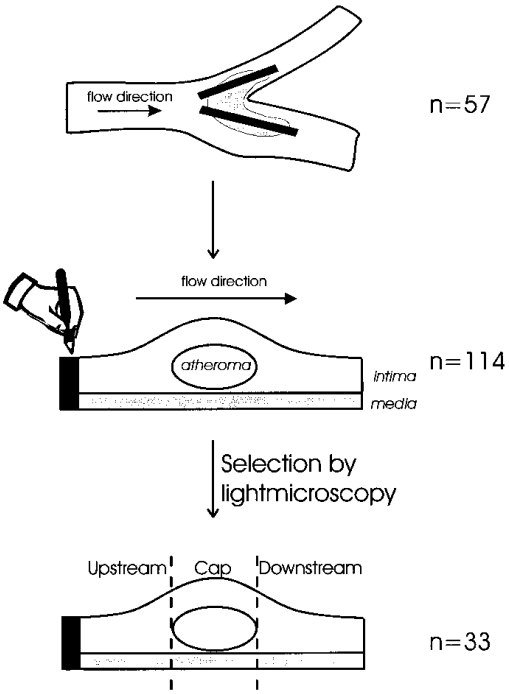
Tissue sampling

Sixty-three left and right carotid artery bifurcations were studied in a consecutive autopsy series of 45 patients (mean age, 69 years; range, 26 to 89 years). In all cases, the postmortem interval was <24 hours. Excluded from the study were immunocompromised patients and patients who had died under septic conditions. Left and right carotid arteries were carefully dissected from the surrounding tissues, and a segment was removed that contained 10 mm of the common carotid artery at the upstream end, the carotid bifurcation, and 10 mm of the internal and the external carotid arteries at the downstream ends. The arterial segment was opened longitudinally along its ventral side, fixed in 4% buffered formalin, and, if necessary, decalcified in EDTA for 4 days. Arteries with total luminal occlusion were excluded; none of the arteries showed recanalization. From the remaining samples, a longitudinal transmural tissue block of ≈20x4 mm was removed from both the internal and external carotid arteries. These tissue blocks were marked immediately with India ink at the upstream (proximal) site to ensure their topographic relation with the flow direction. They were then routinely processed for paraffin embedding and microscopic sectioning (Figure 1).

Light microscopy

Serial sections 6 µm thick were cut parallel to the long axis of the arterial segment, and 2 sections were stained with hematoxylin-eosin and an elastic-van Gieson stain for screening. Arterial segments that appeared to contain diffuse atherosclerosis or fatty streaks, as well as plaque-free segments, were all excluded from the study. Ruptured or eroded plaques were excluded from morphometric evaluation; these plaques were studied to determine at which site of the plaque (upstream or downstream) rupture or erosion had occurred. The remaining

Figure 1. Schematic of sampling and further selection of carotid artery plaques.



segments, containing raised plaques with intact upstream and downstream shoulders and cap parts, were used for further investigation (Figure 1).

Immunohistochemistry

Adjacent serial sections were stained for SMCs with an anti–α-actin antibody (SMA, clone 1A4, DAKO, dilution 1:200). Macrophages were stained with an anti-CD68 antibody (clone PG-M1, DAKO, dilution 1:100). A 3-step indirect streptavidin-biotin technique with peroxidase was used, in which final visualization of the peroxidase activity was performed with diaminobenzidine as chromogen. Nuclei were faintly counterstained with hematoxylin. In negative controls, the primary antibody was replaced by an irrelevant mouse monoclonal antibody of the same subclass.

Morphometry

Surface areas of the upstream (proximal) shoulder and the downstream (distal) shoulder of plaques were planimetrically quantified in tissue sections with image-analysis software running on a PC connected with a video-mounted microscope. The shoulder parts were defined as the plaque area reaching from the adjacent normal intima (upstream or downstream) to the outer sides of the lipid core (atheroma) at both ends (Figure 1). These areas were outlined

manually, and the percentage of immunostained surface was measured automatically with gray-scale detection. In this way, we calculated the anti-CD68 (macrophages) and anti-α-actin (SMC) immunopositive areas as a percentage of the total area of each shoulder part in square millimeters. The ratios of macrophagepositive areas and SMC-positive areas were calculated for each plaque individually. Results were recorded as mean ±SD.

Statistical analysis

For comparison of morphometric data between different plaque areas, which were not compatible with a normal frequency distribution, a paired Student's *t* test with the logarithmic transformation of individual values was used (±SD). Values of $P<0.05$ were considered significant.

RESULTS

Six carotid arteries (10%) were occluded. Histopathological analysis of the carotid artery samples resulted in 41 plaque free segments (36%), 31 segments containing diffuse atherosclerosis (27%), and 9 segments showing rupture or erosion (8%). The site of rupture or erosion was upstream in 6 of the 9 plaques. Each of the remaining 33 carotid artery segments (29%) contained an entire atherosclerotic plaque, and these were used for further study (Figure 2). Immunohistochemistry revealed large variations in the numbers of SMCs and macrophages among plaques of different patients but also within one and the same plaque. Some plaques contained only SMCs, whereas others were almost totally infiltrated by macrophages. On average, however, SMC areas were larger than macrophage areas.

The results of area quantification of SMCs and macrophage areas in the immunostained sections are shown in the Table 1. In 23 of the 33 sections (70%) stained with anti-α-actin, the SMC areas of the downstream (distal) shoulder were larger than those of the upstream shoulder part, with an upstream/downstream ratio [ln (U/D) ratio] of -0.41. In the downstream (distal) shoulder, the SMC areas were significantly larger than in the upstream (proximal) shoulder ($P=0.031$)(Figure 2). In 22 of 33 cases (67%), anti-CD68-stained sections showed larger macrophage areas in the upstream (proximal) shoulder part of the plaque, with a U/D

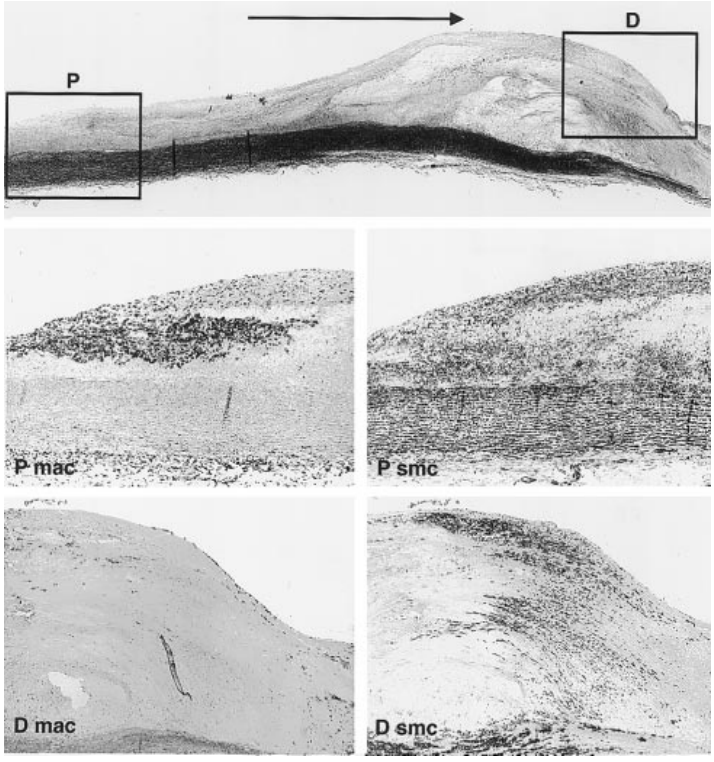
Table 1. Macrophage and SMC Area Quantification in the Upstream and Downstream Shoulder Parts of 33 Atherosclerotic Plaques in the Carotid Artery

Measurements	Upstream	Downstream	*P*-value
Mean measured area, mm^2	2.49 ± 1.81	2.38 ± 1.19	
ln(Mac %)	1.55 ± 1.14	0.81 ± 1.95	0.011
ln(SMC %)	2.56 ± 1.09	2.97 ± 1.08	0.031
ln(Mac %/SMC %)	-1.02 ± 1.51	-2.67 ± 2.53	0.001

Mac indicates macrophage.

ratio [ln (U/D)] of 0.74. Macrophage areas were significantly larger in the upstream shoulder areas of plaques (*P*=0.011)(Figure 2).

Figure 2. Top, Overview of an entire carotid artery plaque. Horizontal arrow indicates direction of blood flow. Boxed area P is in proximal (upstream) shoulder of plaque; boxed area D is in distal (downstream) shoulder. Elastic–van Gieson stain; magnification x12. Middle, Boxed area of proximal (upstream) shoulder stained with anti-CD68 (P mac) and anti–α-actin (P smc); magnification x40. Bottom, boxed area of distal (downstream) shoulder stained with anti-CD68 (D mac) and anti– α -actin (D smc); magnification x40.



DISCUSSION

Several risk factors for atherosclerosis, including hemodynamic factors, may be implicated in determining the cellular composition of plaques. To the best of our knowledge, this is the first study that shows marked topographic variation in cellular composition within atherosclerotic plaques related to the direction of the blood stream. Planimetric quantification of the macrophage contents in carotid plaques showed statistically significantly larger macrophage-rich areas in the upstream shoulder than in the downstream shoulder of the same atherosclerotic lesion. This phenomenon may render the upstream part of an atherosclerotic plaque more vulnerable to erosion or rupture than the downstream part. Indeed, 6 of 9 rupture sites were

upstream. Differences in fluid mechanics at the luminal site of different regions of the plaque could be responsible for differences in plaque architecture.

The carotid artery has been used by several investigators to study the relationship between flow dynamics and plaque formation. Zarins et al[12] and Ku et al[15] showed that the upstream sites of plaques are preferentially under high flow/high shear stress, whereas downstream parts are under low flow/low shear stress. Plaque growth, moreover, has been shown to occur predominantly in regions of low shear stress.[11,12,15-18] A recent angiographic study of femoral arteries also revealed that plaque growth in the downstream direction occurs significantly more frequently than in the upstream direction.[19]

It is known from in vitro studies of endothelial cells under shear stress conditions that high shear stress induces increased expression of endothelial adhesion molecules, such as ICAM and VCAM, resulting in enhanced leukocyte adherence, including monocytes and lymphocytes.[20,21] Conversely, other investigators found a relationship between low shear and macrophage infiltration due to prolonged and intimate contacts between mononuclear cells and the endothelial lining.[11,12] However, in the in vivo situation of human arteries, shear stress may not be the only rheological factor interfering with leukocyte adherence and influx. Recently, Tropea et al[22] studied the differences in monocyte binding upstream and downstream to artificial coarctations in lipid-fed New Zealand White rabbits. They demonstrated that monocyte adhesion and VCAM-1 expression were increased upstream of the stenosis, which resulted in enhanced intimal thickening and accumulation of macrophages at these sites.

Because the common carotid artery conveys blood with high flow and high kinetic energies, one may assume that at sites of atherosclerotic plaques, similar mechanisms are involved, as described by Tropea et al.[22] This, then, could account for the large macrophage-rich areas in the upstream shoulder of the lesions. Nevertheless, the dominant overall cell type in most plaques appeared to be the SMC. In individual plaques, however, the downstream shoulders showed (on average) larger SMC-rich areas than their upstream counterparts. This is of interest because an increase of shear stress activates endothelium-derived nitric oxide (NO) synthase and NO production,[23,24] and a chronic increase in NO has an inhibitory effect on SMC protein synthesis and SMC proliferation.[23,24] In areas with low shear stress, such as the downstream parts, there is no step-up in NO production. In fact, it has been shown that low shear stress increases endothelin production, which acts as a stimulating factor for the production of extracellular matrix components by SMCs and for SMC proliferation.[25] Platelet adherence in low-flow areas, with release of platelet-derived growth factor and basic fibroblast growth factor, could provide another stimulus for SMC growth.[2,26] SMC growth with connective tissue production is generally considered to be the mechanism responsible for a gradually progressive growth of atherosclerotic plaques.[2] These phenomena, therefore, could provide an explanation for the differences in SMC content between the upstream and the downstream parts of plaques and the slowly progressive growth downstream of the main lesion.

Limitations

Obviously, shear stress cannot be the only factor involved. It is likely that a balance between local hemodynamic variables, such as pulse pressure, wall stress, and turbulence, all play a role in the eventual component makeup of an atherosclerotic plaque.[11,12,15-17,27] And because this study is based on specimens obtained at autopsy, without much clinical information, a variety of intrinsic and environmental risk factors for plaque development and growth could have been involved, which could be reflected in variability in macrophage and SMC contents in plaques of different patients. Conversely, one may anticipate that such factors affect the overall composition of plaques rather than inducing local changes. However, it appears from this study that the overall effect of the variables involved in human plaque formation results in increased macrophage infiltration at the upstream site and increased SMC growth at the downstream sites.

CONCLUSION

Our observations in human carotid arteries are of clinical relevance. Plaque instability leading to plaque rupture is considered to be a disbalance between reparative activities (SMC growth and collagen synthesis) and degrading activities induced by macrophages.[1,7,8] Therefore, the large amounts of macrophages in the upstream parts of plaques could indicate a relationship between high flow/high shear stress and plaque instability.

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CHAPTER 3

A COMPARATIVE ANALYSIS OF ELECTROCARDIOGRAPHY AND CORONARY ANGIOGRAPHY FOR THE DETERMINATION OF THE CULPRIT SEGMENT IN ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Objective It has been claimed that localization of the culprit coronary segment can be predicted based on electrical vector theory of the ST-segment deviation on the electrocardiogram (ECG). These criteria are based on theories and non-blinded studies and there is a need for evaluation in a clinical, prospective and blinded setting.

Methods Patients (n=153) with a STEMI undergoing emergency coronary angiography were included in the analysis. Localization of the culprit coronary segment was based on electrical vector theory of the ST-segment deviation rather than a ST-segment deviation score compared to the verification of the culprit segment at coronary angiography.

Results The correct culprit coronary segment was identified in 39%. The sensitivity and specificity to detect a proximal site of occlusion in the coronary artery in the total study population was 47% and 57%, respectively, in anterior STEMI this was 31% and 67%, respectively.

Conclusion The interpretation of the ECG to predict the exact site of coronary occlusion based on electrical vector theories appeared to be not very accurate and showed low sensitivity and specificity values. These findings underscore the importance of immediate coronary angiography in patients with the typical clinical presentation of acute MI and any degree of ST-segment elevation.

INTRODUCTION

The typical presentation of an acute myocardial infarction (MI) is a patient presenting with sudden onset of chest pain, discomfort and/or dyspnoe, with or without radiation and/or vegetative symptoms that lasts for at least twenty minutes. The clinical diagnosis is based on these complaints in combination with electrocardiographic changes. More than 100 years after Einthoven's publication of the electrocardiogram (ECG),[1] the ECG has become indispensable for rapid diagnosis and management of patients with a wide variety of cardiac diseases, including ST-segment elevation MI (STEMI).[2] The ECG is easily available, non-invasive, inexpensive and crucial in the diagnosis of acute MI. The criteria for STEMI are new or presumed new ST-segment elevations at the J point in two or more contiguous leads with the cut-off points ≥0.2mV in men or ≥0.15mV in women in leads V2-V3 and/or ≥0.1mV in other leads.[3] The ECG not only indicates the presence of a STEMI, but can also be used for localization and extent of the jeopardized area.[4] Among others, the area at risk is one of the major prognostic determinants for final infarct size, dependent on the site of occlusion in the coronary artery tree.[5]

Direct verification for the site of coronary occlusion in acute MI is obtained by emergency coronary angiography (CAG). ECGs can be analysed by computerized algorithms, but interpretation by a experienced cardiologists, aware of the strengths and limitations of the ECG,

is the golden standard. It has been claimed that localization of the infarct related coronary artery and culprit coronary segment can be predicted based on electrical vector theory of the ST-segment deviation from the isoelectric line in the 12-lead ECG.[6,7]

The electrical vector theory for determining the site of occlusion in the coronary artery has been described extensively:[6-11] In STEMI the direction of both ST-segment elevation and reciprocal ST-segment depression is determined by the direction and magnitude of all ST-segment deviations resulting in a main vector in the direction of the most pronounced ischaemia. This vector indicates the site of occlusion in the coronary artery. In inferior wall MI an occlusion of the right coronary artery (RCA) will result in an inferior and rightward orientated ST-segment vector, whereas an occlusion in the circumflex coronary artery (CX) will result in an inferior and leftward oriented vector. In anterior wall MI the ST-segment vector will point in a superior direction in proximal occlusion of the left anterior descending coronary artery (LAD), in contrast to the more inferiorly pointed vector in case of a more distal occlusion (distal to the first diagonal and septal branches). This and additional criteria are described in more detail by others.[6-11]

However, these criteria are mainly based on (electrical vector) theories or on non-blinded studies and there is a need to evaluate this in clinical practice in a prospective and blinded setting. To examine the ECG in STEMI in relation to CAG we asked a cardiac electrophysiologist, blinded for CAG, to analyze a series of ECGs by using the electrical vector theory.

PATIENTS AND METHODS

From 1999 to 2003 ECGs were collected from patients with a STEMI in the Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands. The patients were all treated with primary angioplasty as part of different trial protocols enrolled at our institute.[12-14] Enrolment in the trials was guided by in- and exclusion criteria that included a classical presentation and ST-segment elevation. The patients participating in these trials were included in the current analysis, provided that the ECG prior to CAG and patient data were available. Patients in whom an inferior infarct was present were only included when V4R was available.

For interpretation of the ECGs we asked an established cardiac electrophysiologist to judge the last ECG before CAG to predict the localization of the culprit coronary segment based on ECG and the following patient characteristics: age, sex, time of chest pain to ECG and location of previous MI. Localization of the culprit coronary segment was based on electrical vector theory of the ST-segment elevation as described by others[6-11] rather than on the ST-segment deviation score. The coronary segments were depicted on a coronary artery tree according to the American Heart Association (AHA) classification.[15] In case it was not possible to make a definite decision by electrocardiographical analysis a comment was required.

The CAGs were analyzed for infarct site location by two interventional cardiologists (ER, MP). In anterior MI the position and size of the first diagonal and septal branches was analyzed.

Data were presented as mean ±SD, and for non-parametric measurements as median with percentiles (P25 and P75). For discrete variables a Chi-square test was used. T-tests were performed provided that data were not skewed. The Mann-Whitney-U test was used for non-parametric analysis. Significance was defined as $P<0.05$. Sensitivity and specificity values were calculated for the total study population and subgroups (anterior wall STEMI and extensive ST-segment deviation (>median sum of ST-segment deviation)) related to a proximal or distal coronary occlusion at CAG. A secondary analysis was performed in cases the analysis of the ECG indicated the direct adjacent coronary segment next to the culprit segment.

RESULTS

Electrocardiographical analysis

From 280 patients presenting with a STEMI enrolled in clinical trials, 153 were included in the current analysis. Patients were excluded due to incomplete data sets (unavailability of ECGs with V4R or unavailability of ECGs prior to angiography). The baseline characteristics are shown in Table 1. The median sum of ST-segment deviation was 18mm, this was significantly different between anterior wall and inferior wall MI.

Analysis of the ECG indicated the RCA as the infarct related artery 33 times; the CX in 6 patients; the LAD was scored in 89 patients. For proximal and mid LAD lesions the site in relation to first septal and diagonal branches was stated when feasible. Of the 34 times segment 6 was scored, 29 were scored as being proximal to S1 and D1, and 5 times the occlusion was scored to be proximal of S1, though distal to D1. Conversely, for segment 7 the lesion was

Table 1. Baseline characteristics

Characteristics	Total N = 153 (%)	Anterior MI N = 105 (%)	Inferior MI N = 48 (%)	*P*-value
Mean age (+/- SD)	61 (+/-13)	60 (+/-13)	63 (+/- 13)	0.141
Male	114 (75)	84 (80)	30 (63)	0.028
Diabetes Mellitus	18 (12)	13 (12)	5 (10)	0.794
Hypercholesterolaemia	32 (21)	21 (20)	11 (23)	0.674
Hypertension	34 (22)	20 (19)	14 (29)	0.208
Current Smoker	88 (58)	60 (57)	28 (58)	1.000
Family history	38 (25)	24 (23)	14 (29)	0.425
Median sum of ST-elevation [P25-P75]	13 [8.5-20]	15 [10-22]	10 [7-15]	<0.001
Median sum of ST-deviation [P25-P75]	18 [11-24]	19 [11-25]	18 [13-23]	0.923
Previous MI	1 (0.7)	1 (1)	0	1.000
Previous PCI	8 (5)	6 (5.7)	2 (4.2)	1.000
Previous CABG	0	0	0	-

MI = myocardial infarction; SD = standard deviation; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft

scored to be distal to S1 and proximal to D1 in 37 cases, versus 16 cases in which the lesion was scored to be distal to both D1 and S1. In the remaining 25 cases it was not possible to make a definite prediction, because of various reasons: in 17 of these because of insufficient ST-segment elevation (mainly in limb leads), the remaining because of intrusion and absence of sinus rhythm.

Angiographical analysis

All 153 angiographies were suitable for analysis and in none of the cases there was disagreement between the two interventional cardiologists. The culprit segment was in the RCA in 35 cases, in the CX in 13 cases, and the LAD was the culprit coronary in the remaining 105 cases. Coronary anatomy was variant in 16 cases. Concerning segment 7: Anatomy was variant in 8 patients; S1 much larger than S2 (4 cases), S1 much smaller in size than the S2 (8 cases), a large D1 (2 cases), and a much larger D2 compared with the D1 (4 cases).

Primary analysis (Tables 2-4)

The results per coronary segment are shown in Table 2. Overall, the correct culprit coronary segment was indicated by analysis of the ECG in 39% (n=60) of cases. To specify, in patients with an anterior wall infarction the correct segment was scored in 36% (38/105) versus 46% (22/48) in inferior wall infarctions (Table 3). Underestimation (24%) was present when analysis

Table 2. Crosstabulation: Prediction of culprit lesion by ECG analysis (horizontal) versus angiography (vertical)

CAG \ ECG	1	2	3	4	5	6	7	8	9	10	11	12a	12b	13	14	15	16	No definite prediction	Total
1	**17**													1				1	19
2	8	**3**																1	12
3	2		**0**															2	4
4				-														-	0
5					-													-	0
6						**16**	28			1								9	54
7						16	**21**											8	45
8						1	3	**1**										0	5
9							1		**0**									0	1
10										-								-	0
11	1										**2**			1				2	6
12a									1			**0**						0	1
12b						1							**0**					1	2
13	1										1			**0**				0	2
14											1				**0**			0	1
15	1															**0**		0	1
16																	-	-	0
Total	30	3	0	0	0	34	53	1	1	1	4	0	0	2	0	0	0	24	153

Coronary segment classification according to the American Heart Association.[16]

Bold numbers indicate a correct prediction of the culprit coronary segment in absolute numbers by analysis of the ECG.

Table 3. Primary analysis

Variable	Total (%)	Correct (%)	Underestimated (%)	Overestimated (%)	No definite prediction
Anterior MI — no. (%)	105 (69)	38 (36)	29 (28)	21 (20)	17 (16)
Inferior MI — no. (%)	48 (31)	22 (46)	7 (15)	14 (29)	5 (10)
Total — no. (%)	153 (100)	60 (39)	36 (24)	35 (23)	22 (14)
Coronary Segment — no. (%)					
1	19 (12)	17 (89)	1 (5)	n.a.	1 (5)
5 or 6	54 (35)	16 (30)	28 (52)	n.a.	10 (19)
11	6 (3,9)	2 (33)	1 (17)	n.a	3 (50)
All proximal lesions	79 (52)	35 (44)	30 (38)	n.a.	14 (18)

MI = myocardial infarction; n.a. = not applicable; coronary segment classification according to the American Heart Association.[16]

Table 4. Cross tabulations and sensitivity/specificity calculation

Variable	CAG proximal	CAG distal	Total
Total study population	N	N	N
ECG proximal	37*#	32	69
ECG distal or no definite prediction	42	42	84
Total	79	74	153
Sensitivity / Specificity	47% / 57%		
Subgroup Anterior MI			
ECG proximal	17*	17	34
ECG distal or no definite prediction	37	34	71
Total	54	51	105
Sensitivity / Specificity	31% / 67%		
Subgroup Inferior MI			
ECG proximal	20#	15	35
ECG distal or no definite prediction	5	8	13
Total	25	23	48
Sensitivity / Specificity	80% / 35%		
Subgroup >18mm ST-segment deviation			
ECG proximal	24#	13	37
ECG distal or no definite prediction	20	19	39
Total	44	32	76
Sensitivity / Specificity	55% / 59%		
Subgroup <18mm ST-segment deviation			
ECG proximal	13*	19	32
ECG distal or no definite prediction	22	23	45
Total	35	42	77
Sensitivity / Specificity	37% / 55%		

*One case: At ECG segment 5 or 6, at CAG segment 6; #One case: At ECG segment 1, at CAG segment 11; CAG = coronary angiogram; ECG = electrocardiogram; MI = myocardial infarction

of the ECG indicated a more distal segment than on CAG, and overestimation (23%) when it was more proximal segment at CAG. In the 16 cases with variant coronary anatomy the culprit segment was correctly indicated in 10 cases. In case of a proximal occlusion (coronary segment 1, 5, 6, or 11) the correct segment was scored in 44%, in 18% there was no segment pointed out as site of occlusion.

The median sum of ST-segment elevation was higher in the group in which the prediction was correct, 15mm [P25-P75;10-21] versus 11mm [P25-P75;8.0-19](*P*=0.057). The median sum of ST-segment deviation was significantly higher in the group in which the prediction was correct, 21mm [P25-P75;14-27] versus 16mm [P25-P75;9.0-23](*P*<0.001). In the total study population and in subgroups sensitivity en specificity values were calculated from cross tabulations (Table 4). The sensitivity to detect a proximal site of occlusion in the coronary artery in the total study population, in the subgroups anterior wall MI and extensive ST-segment deviation were 47%, 31% and 55%, respectively. The specificity to a proximal site of occlusion in the total study population, in the subgroups anterior wall MI and extensive ST-segment deviation were 57%, 67% and 55%, respectively.

Secondary analysis (Table 5)

Analysis of the ECG indicated the site of occlusion at the adjacent coronary segment in 55 cases. Consequently, the culprit or the adjacent coronary segment was correctly indicated in 75%. In case of a proximal occlusion the prediction of the exact coronary segment was correct in 80%. The median sum of ST-segment elevation was higher in the group in which the prediction was correct, 15mm [P25-P75;10-22] versus 8.5mm [P25-P75;5.0-11](*P*=0.057). The median sum of ST-segment deviation was significantly higher in the group in which the prediction was correct, 20mm [P25-P75;14-27] versus 11 mm [P25-P75;6-18](*P*<0.001). The sensitivity in the total study population, in the subgroups anterior wall MI and extensive ST-segment deviation were 47%, 31% and 55%, respectively. The specificity in the total study population, in the subgroups anterior wall MI and extensive ST-segment deviation were 57%, 67% and 55%, respectively.

Table 5. Secondary analysis

Variable	Total (%)	Correct (%)	No definite prediction
Anterior MI — no. (%)	105 (69)	85 (81)	17 (16)
Inferior MI — no. (%)	48 (31)	30 (63)	5 (10)
Total — no. (%)	153 (100)	115 (75)	22 (14)
Coronary Segment — no. (%)			
1	19 (12)	17 (89)	1 (5)
5 or 6	54 (35)	44 (81)	10 (19)
11	6 (3,9)	2 (33)	3 (50)
All proximal lesions — no. (%)	79 (52)	63 (80)	14 (18)

MI = myocardial infarction; coronary segment classification according to the American Heart Association.[16]

Time

There was no indication that the duration of ischemia was of influence. The median time from onset of symptoms to the ECG was 131 minutes (P25-P75;87-199), and not significantly different in patients in which the prediction was incorrect (*P*=0.317). The median time from last ECG to first CAG was 61 minutes (P25-P75;27-95).

DISCUSSION

Overall analysis of the ECG indicated the correct culprit coronary segment in 39% (60/153). In almost a quarter of the cases there was an underestimation of the area at risk. Consequently, in the total study population and in all subgroups the sensitivity and specificity values were low to detect a large area at risk due to a proximal location of coronary occlusion. If analysis of the ECG is confined to cases with extensive ST-segment deviation (>18mm) the sensitivity and specificity remained low, 55% and 59%, respectively. It appeared that the ECG is not an accurate diagnostic tool for exact prediction of site of occlusion in the infarct related coronary artery, that reflects the area at risk, even when interpreted by a cardiac electrophysiologist. However, the secondary analysis showed that in case the analysis of the ECG was incorrect the direct adjacent coronary segment was indicated as the culprit lesion in 35% (53/153) cases, leading to a 75% accurate prediction. It is clear that the ECG interpretation in combination with clinical presentation remains the investigation of choice for the diagnosis of acute MI. The current analysis showed that a considerable amount of patients with proximal lesions, responsible for a large area at risk, may not show distinct ST-segment elevations at the ECG. This may have implications for the choice of treatment e.g reperfusion therapy by thrombolysis or primary PCI versus non-invasive therapy. Especially in the case when a clinician must decide between thrombolysis or primary PCI underestimation of area at risk on ECG alone can lead to undertreatment. Therefore, analysis of the ECG should not be used to decide the treatment strategy in STEMI.

The question remains why the analysis of the ECG scored suboptimal. In a large proportion of the cases (14%) the ECG did not show sufficient ST-segment elevation to make an accurate prediction of the exact site of occlusion. Despite the fact that the majority of patients included had a STEMI caused by a large area of jeopardized myocardium in a large epicardial vessel eligible for acute PCI. For accurate interpretation of the ECG it appears to be essential that there is sufficient ST-segment deviation. This can partly be explained by the dynamic occlusions in case of a acute MI, which in a large proportion is caused by a thrombotic occlusion. In these cases a coronary vessel may not be totally occluded the entire time and collateral flow may also vary in time in the setting of an acute MI. In other patients a proximal coronary lesion causes embolization occluding a distal part of the coronary vessel. This is also indicated by the observation that although the inclusion ECG for the trials all showed significant ST-segment

elevation, the analyzed ECGs were not eligible for proper analysis in 16%, mainly because the ECG did not show enough ST-segment elevation (mainly in limb leads). This ST-segment resolution may reflect the dynamics of an epicardial occlusion and may indicate an effect of pharmacological treatment with aspirin, clopidogrel, heparin and in some cases glycoprotein IIb/IIIa receptor blockers routinely administered prior to CAG in case of a STEMI. It may also be hypothesized that ST-segment deviation decreases the longer ischaemia is present, although in this analysis the difference in time from onset of symptoms to ECG did not change outcome.

Secondly, coronary anatomy is clearly not similar in every patient and this could very well be responsible for failure of localization by vector theory alone. This is especially important when trying to differentiate between the proximal LAD lesions, e.g. between segment 6 and 7. Moreover, in 15 patients the first diagonal or septal branches were not comparable in size, thereby notably influencing the vector of ischemia.

Thirdly, it was recently shown by cardiac magnetic resonance imaging that the assumed coronary ECG correlations may vary greatly depending on size and dependent on morphology of the thorax and positioning of the heart in the thorax.[16]

Limitations

Limitations of the current analysis is the retrospective nature of the trial and the amount of ECGs analyzed for different angiographic acute MI's. In a several patients the data or ECGs were not unavailable for currents analysis, this may have led to bias. The inclusion of inferior wall MI's was limited mainly due to unavailability of an ECG with V4R registration. Therefore, the results in from patients with inferior wall MI should be interpreted with some caution. However there is no reason to expect improved sensitivity or specificity values in inferior wall infarction in larger study populations. Because of the nature of the trials from which we collected data acute MI's were limited to stentable culprit lesions with at least a 2,5mm stent. It is conceivable that this caused the finding of a majority of culprit lesions in proximal part of the coronary arteries and the LAD. The ECGs were analyzed by one electrophysiologist, however based on vector theory and algorhythms that were extensively described before. We didn't measure the amount of collateral flow or the area at risk. Finally, angiographical determination of culprit lesion might not relate well to final infarct size or actual area at risk in all patients.

CONCLUSION

The ECG interpretation in combination with clinical presentation remains the investigation by choice for the diagnosis of acute myocardial infarction. In practice a single ECG appeared to be inaccurate for exact prediction of the infarct related coronary segment, hence a reflection

of the area at risk, even when interpreted by an electrophysiologist. Large areas at risk in acute MI can be accompanied by ECGs with small amounts of ST-segment deviation in a considerable amount of patients. The findings of this study underscore the importance of immediate coronary angiography in patients with the typical clinical presentation of acute myocardial infarction and any degree of ST-segment elevation.

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CHAPTER 4

EARLY DISCHARGE FOLLOWING PRIMARY PCI WITH STENT IMPLANTATION VIA THE RADIAL ARTERY UNDER PLATELET GLYCOPROTEIN IIB/IIIA RECEPTOR BLOCKADE

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ABSTRACT

Background Primary percutaneous coronary intervention (PCI) with stent implantation demonstrated to be superior to both PCI with balloon angioplasty and to thrombolysis for acute ST-segment elevation myocardial infarction (STEMI). The use of glycoprotein (GP) IIb/IIIa blockers in this setting may be beneficial. However, GP IIb/IIIa receptor blocker treatment is frequently accompanied by femoral entry site-related bleeding complications, resulting in additional morbidity and prolonged hospitalization. These complications are minimized by using the transradial approach (TRA).

Methods This study prospectively explored the feasibility of early discharge (within 4 days) following primary PCI with transradial stent implantation under GP IIb/IIIa blockade with tirofiban in the setting of STEMI. One-hundred patients with STEMI eligible for PCI were included.

Results Of these 100 patients, 62% received treatment according to the protocol, *e. g.*, TRA, successful PCI with stent implantation, fulldose GP IIb/IIIa receptor blocker infusion and early discharge. The PCI was successful in 95%. Early discharge was achieved in 75 patients of the total study population. Major adverse cardiac and cerebral events (MACCE) did not occur in the early discharge group, with a 1-year event-free survival rate of 91%. The combined MACCE rates in the total study population at 1, 6, and 12 months were 8%, 15% and 20%, respectively.

Conclusion Early discharge is feasible following primary PCI with stent implantation via the radial artery under GP IIb/IIIa blockade for STEMI, however a larger study is needed to prove the efficacy of this strategy.

INTRODUCTION

Primary percutaneous coronary intervention (PCI) with stent implantation demonstrated to be superior to balloon angioplasty and thrombolysis in patients suffering from an acute ST-elevation myocardial infarction (STEMI) by reduction of the occurrence of major adverse cardiac (and cerebral) events (MACCE).[1-3]

In addition, recently the RAPPORT, ISAR-2, ADMIRAL and CADILLAC trials have documented further improvement in outcomes after primary PCI when abciximab is added to the regime.[4-7] Although to date not yet proven to be beneficial as an adjunct to PCI for STEMI, the widely-used and cheaper GPIIb/IIIa receptor blocker, tirofiban, has shown to be beneficial in the setting of unstable angina pectoris by reduction of thrombotic events.[8,9] Moreover, the TARGET Trial demonstrated that long-term outcomes did not differ between abciximab and tirofiban in patients with unstable angina pectoris.[10]

However, it is well recognized that predominantly entry site-related bleeding complications are a frequent companion of GP IIb/IIIa blocker treatment (12% in the ADMIRAL Trial), resulting in additional morbidity and prolonged hopitalization.[11,12] By using the tranradial approach (TRA) for arterial access, local bleeding can be minimized.[13] The applicability of the TRA for primary PCI with GP IIb/IIIa receptor blockers in STEMI has been described earlier.[14-16] The TRA provides a safe and possibly favorable alternative to primary PCI via the transfemoral approach (TFA) and the TRA.[14,17,18]

Early discharge may be achieved by the combined strategy of early reperfusion resulting in reduction of infarct size, with concomitant reduction in complications (e. g., congestive heart failure), and the use of a safe entry site.[19] Additionally, the treating physician benefits from the angiographically-acquired information on the patient's coronary anatomy. Reduction of the patient's hospital stay is not only generally well appreciated by patients, it also has advantages for the hospital and cardiology departments since it allows effective use of hospital capacity and resources.[20] The present prospective trial was conducted in order to evaluate the feasibility of our strategy of early discharge after transradial stent implantation and GP IIb/IIIa blockade in the setting of STEMI.

METHODS

This clinical study was a prospective, open, nonrandomized, single-center study designed to assess the feasibility of early patient discharge after transradial stent implantation under GP IIb/IIIa blockade in the setting of STEMI. All interventions were executed by four high-volume operators experienced in interventions by the TRA. Written, informed consent was obtained from all participating patients before intervention. The study design and protocol were approved by the institutional ethics committee.

Patient selection

Consecutive patients between 18 and 80 years of age with STEMI (≥20 minutes of chest pain and electrocardiographic (ECG) signs of STEMI (≥1 mV ST-segmentelevation in ≥2 contiguous leads) were included in the trial. Patients had to be eligible for primary PCI and treatment with GP IIb/IIIa receptor blockers. Both treatments had to be established within 6 hours of symptom onset. Exclusion criteria were: 1) history of intractable hypertension; 2) (failed) thrombolysis prior to PCI; 3) poor palpable radial pulse, e. g., cardiogenic shock; 4) contraindication to tirofiban, aspirin or clopidogrel; 5) participation in another clinical study interfering with this protocol.

Medication

Following consent, the patient received tirofiban (Aggrastat, MSD) intravenously (IV) at the earliest possible moment after presentation at the hospital: 0.4 µg/kg/minute bolus of 30 minutes followed by 0.1 µg/kg/minute up to 12 hours after the procedure. Patients with renal failure (screening serum creatinine >2.48 mg/dL) received 0.05 µg/kg/minute following the bolus injection. Patients not on daily aspirin received at least 300 mg orally before the intervention, and this was continued (100 mg once daily). As soon as possible, the patients were transferred to the catheterization laboratory. After sheath insertion, 10,000 IU of heparin and 900 mg aspegic were administered. The administration of verapamil or nitroglycerin in the radial artery was at the discretion of the operator. In the event of stent implantation, clopidogrel was given at a loading dose of 300 mg after PCI followed by 75 mg/day for 4 weeks. Heparin infusion (1,000 IU/hour) was started 6 hours after the intervention and was continued for 12 hours in total, irrespective of APTT.

Angioplasty and stent implantation

The radial approach was used if the radial artery was palpable and the Allen's test was positive. In all instances, 6 Fr guiding catheters were used. The insertion site for both the radial as well as the femoral approach were prepared before beginning the procedure in all patients in order to limit procedural time in case there was crossover from the radial to the femoral approach. The target coronary segment was projected in two orthogonal planes. Balloon dilatation and stent implantation were performed according to current practice.

Assessment of angiographical result

A final angiogram was made in the same views following a bolus of 100-200 µg intracoronary nitroglycerin. Quantitative coronary analysis (QCA) was performed. An optimal PCI result was defined as a diameter stenosis (DS) <50%, and improvement of TIMI flow of at least two grades, or TIMI flow grade 3.

Laboratory

After admission, total creatine phosphokinase (CK) and CK-MB were repeated every 6 hours (3-4 times). For infarct size estimation, the peak values of CK-MB and CK were used.

Hemostasis and sheath removal

Immediately following the procedure, the radial sheath was removed in all instances, followed by application of a compressing bandage which was removed 4 hours after termination of the tirofiban infusion. In cases where the transfemoral approach was used, the sheath was removed 4-6 hours after cessation of the heparin infusion, followed by application of compressing bandage for 4-6 hours. Vascular closure devices were not used.

Discharge

Following a successful procedure, the "early" mobilization scheme was used[19]: Day 0: Bed rest, sitting up in bed. Day 1: Transfer from the coronary care unit to the cardiology ward. Sitting up. Personal hygiene (standing by the bedside). Day 2: Walking across the ward (up to 100 meters). Day 3: Walking stairs (and up to 500 meters). End of day 3, or for logistic reasons, early morning of day 4: discharge. Reasons for prolonged hospital stay were recorded and scored: 1) vascular access site complication; 2) heart failure requiring optimal therapy; 3) postinfarct angina; 4) occurrence of troublesome arrhythmias; 5) medical condition not related to cardiac illness; 6) social reasons, e. g., patients in poor social circumstances (dependant, poor mental status).

Safety and feasibility

Safety was assessed as the occurrence of major adverse cardiac and cerebral events (MACCE) and bleeding complications. MACCE included death of any cause, recurrent myocardial infarction (MI), repeat revascularization of any vessel or target vessel (TVR) by coronary artery bypass grafting (CABG) or PCI, recurrent angina or stroke (ischemic or hemorrhagic). Major bleeding was defined as any bleeding requiring blood transfusion or additional surgery, continuous bleeding or iatrogenic aneurysm of the entry site artery, or any HB drop >3.2 g/dL; minor bleeding was defined as any bleeding complication or hematoma not requiring blood transfusion or surgery. The following ranking scale was used: 1 = death; 2 = stroke; 3 = MI; 4 = CABG; 5 = PCI of target vessel; 6 = any PCI; 7 = CAG.

Follow-up

The day following discharge and one week after discharge, the patient was interviewed by telephone, and at 1, 3, 6 and 12 months, the patient visited the outpatient department according to routine protocol. If an outpatient visit was made at a referring center, data were retrieved. In the event that data were missing, information was obtained from the outpatient clinic's charts and correspondence.

Statistics

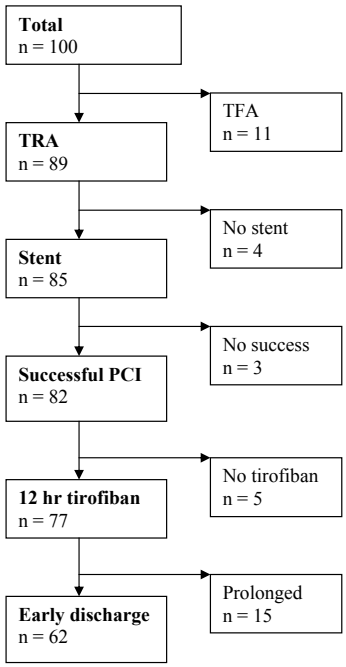
It was stated that with the proposed sample size of 100 consecutive patients, insight could be obtained on the eligibility for this investigational approach in a cohort of patients referred for primary PCI. Continuous data are presented as mean (±SD), in the event that there were skewed data in median values with quartiles (P25-P75). The degree of skewing of data was calculated with SPSS 11.5 for windows, with a cutoff point of skewing >1 or <-1.

RESULTS

Baseline clinical characteristics

From October 1999 to February 2001, 100 patients were recruited who presented to the Amsterdam Department of Interventional Cardiology or were transferred for a primary PCI. The flow chart (Figure 1) illustrates the patients' stratification according to the protocol's pre-defined steps. Sixty-two patients received full treatment according to the protocol. Baseline characteristics are shown in Table 1. The mean time from the start of chest pain to balloon procedure was 3.4 (SD ±1.1) hours.

Figure 1. Patient stratification according to the treatment protocol. TRA = transradial approach; TFA = transfemoral approach; PCI = percutaneous coronary intervention.



Angiographic and procedural data

The angiographicaldata are summarized in Table 2. From the total study population, 89 patients underwent a successful TRA (Figure 1). Of the remaining 11 patients, 3 were primarily approached via the femoral artery, and in 8 patients, radial access was not successful due to various reasons such as severe arterial spasm, marked tortuosity of the radial/brachial artery, anatomical anomalies and weak arterial pulse. Hence, these patients were treated via the femoral artery approach. The mean duration of the procedure was 35 minutes (SD ±19.6) and was not prolonged in patients in which it was necessary to cross over from the TRA to the TFA.

Table 1. Baseline clinical characteristics

Characteristics	Total N = 100
Age (SD)	59 (14)
Hypercholesterolaemia	21
Hypertension	18
Peripheral vascular disease	4
Family history	32
Current smoker	57
Diabetes mellitus	8
Previous MI	9
Q/non-Q-wave	2/7
Previous PCI	4
Previous CABG	1
MI on ECG	
1-Anterior/ lateral/ anterolateral	69
2-inferior	10
3-true posterior	0
4-inferoposterior	21
5-associated RV-infarct	19
Pain-to-balloon in hours (SD)	3,4 (1,1)

MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; ECG: electrocardiogram; RV: right ventricle.

Procedural data are shown in Table 3. Stent placement was successful in 96 patients (Figure 1), stent sizes ranged from 2.5 to 4.0 mm in diameter and 12 to 29 mm in length. The median postprocedural stenosis, assessed by QCA, was 9.0% (quartiles 1.4-17.4%). Overall procedural success was achieved in 95 patients (95%)(Figure 1). Finally, 77 patients underwent successful PCI with transradial stent implantation followed by the full dose of tirofiban (Figure 1).

Hospital phase

The median (quartiles) infarct size estimated by the peak CK and CK-MB was 1,711 (759-3,630) U/L and 182 (84-346) U/L, respectively. Ninety-one patients received a continuous infusion of tirofiban for 12 hours (Figure 1). Two patients died within 12 hours due to the initial infarction, and thus did not receive the full dose of tirofiban. In the remaining 7 patients, tirofiban was discontinued because of bleeding complications. One of the patients in the TRA group experienced a significant access site complication (avulsion of the radial artery), which was treated conservatively. Two patients required blood transfusions for a HB-drop due to femoral entry site bleeding complications. None of the patients suffered a stroke (hemorrhagic or ischemic).

Table 2. Baseline angiographical data

Angiographical data	Total N = 100
Femoral primary	3
Femoral secondary	8
1-vessel disease	72
2-vessel disease	18
3-vessel disease	10
Infarct related artery	
LM	1
LAD	62
RCX	4
RCA	31
SVG (on left coronary)	1
TIMI flow grade	
0/1	75
2	13
3	12
Mean ref diameter (SD)	2,95 (0,58)
Median MLD (quartiles)	0,0 (0,0-0,39)
Median DS % (quartiles)	100 (87-100)
Visual thrombus	72

TRA: transradial approach; LM: left main; LAD: left anterior descending; RCX: ramus circumflexus; RCA: right coronary artery; SVG: saphenous venous graft; TIMI: Thrombolysis in Myocardial Infarction; Ref: reference; MLD: mean luminal diameter; DS: diameter stenosis.

Table 3. Procedural parameters

Parameters	Total N = 100
Dissection	12
Stent	96
Mean size in mm (SD)	3,16 (0,34)
Mean length in mm (SD)	17,91 (4,78)
Post-stent dilatation	28
Additional stenting	30
TIMI flow grade	
0/1	1
2	9
3	90
Procedural success	95
Mean ref diameter (SD)	3,09 (0,56)
Median MLD (quartiles)	2,80 (2,41-3,14)
Median DS% (quartiles)	9,03 (1,44-17,43)

TIMI: Thrombolysis in Myocardial Infarction; ref: reference; MLD: mean luminal diameter; DS: diameter stenosis.

Discharge

Seventy-seven patients in the study population underwent a successful PCI with stent implantation through the radial artery followed by 12 hours of tirofiban infusion. Fifteen of those patients could not be discharged within 4 days, despite a successful PCI (Figure 1), 1 because of a major vascular access site complication, 8 due to heart failure requiring inhospital treatment, 3 due to recurrent anginal complaints, of which 1 eventually died, and 2 were referred for CABG. An additional 3 patients remained in the hospital due to social and logistical reasons.

Follow-up

Early discharge (3-4 days after admission) was achieved in 75 patients of the total study population (Figure 1). The early clinical follow-up data on these early discharge patients are

Table 4. Short-term follow-up in early discharged patients.

Events	Discharge to 1 day N = 75 (%)	1 day to 1 week N = 75 (%)	1 week to 1 month N = 75 (%)
Problems	2 (3)	5 (7)	
Reasons			
1. vascular complication	0	0	
2. angina	0	1 (1)	
3. dyspnoe	2 (3)	3 (4)	
4. death	0	0	
5. stroke	0	0	
6. other medical problems	0	1 (1)	
7. social problems	0	0	
Anginal class (CCS)			
I/IV	62 (100)	58 (98)	72 (99)
II/IV	0	0	1 (1)
III/IV	0	1 (2)	0
IV/IV	0	0	0
No info	13 (17)	16 (21)	2 (3)
Sub-acute closure	0	0	0
Re-CAG	0	0	0
Repeat PCI	0	0	0
Target restenosis	0	0	0
Re-MI	0	0	0
CABG	0	0	0
Death	0	0	1 (1)
Stroke	0	0	0

Events = Ranked. In case of death no anginal status scored.

Re-CAG: recurrent coronary angiography; PCI: percutaneous coronary intervention; Re-MI: recurrent myocardial infarction; CABG: coronary artery bypass graft.

shown in Table 4. Of those patients who were discharged early, 2 experienced minor problems (dyspnea) the first day after discharge. Five patients experienced minor problems within the first week after discharge, while none required additional treatment or additional analysis. The anginal classes of the patients according to the Canadian Cardiovascular Society (CCS) classification at 1 day, 1 week and 1 month were class I/IV in 100%, 98% and 99%, respectively. Clinical follow-up data are shown in Table 5. Of those patients who were discharged early after an uncomplicated hospital stay, the mortality rates at 1 month, 6 months and 1 year were 1%, 3%, and 3%, respectively. For combined MACCE, the rates at 1 month, 6 months and 12 months for the patients who were discharged early were 1%, 5%, and 9%, respectively. Mortality rates (including hospital phase) in the total study population at 1 month, 6 months and 1 year were 4%, 5% and 6%, respectively. The combined MACCE rates in the total study population at 1, 6, and 12 months were 8%, 15% and 20%, respectively.

Table 5a. Ranked follow-up (hospital phase included) in early discharged patients.

Events	1 month N = 75 (%)	6 months N = 75 (%)	12 months N = 75 (%)
Sub-acute closure	0	0	0
Re-CAG	0	0	3 (4)
Repeat PCI	0	0	0
Repeat PCI of target vessel	0	2 (3)	2 (3)
Re-MI	0	0	2 (3)
CABG	0	0	1 (1)
Death	1 (1)	2 (3)	2 (3)
Stroke	0	0	0
Combined	1 (1)	4 (5)	7 (9)

Table 5b. Ranked follow-up (hospital phase included) in total study population.

Events	1 month N = 100 (%)	6 months N = 100 (%)	12 months N = 100 (%)
Sub-acute closure	0	0	0
Re-CAG	0	0	3
Repeat PCI	0	1	2
Repeat PCI of target vessel	2	4	4
Re-MI	1	2	4
CABG	1	2	3
Death	4	5	6
Stroke	0	1	1
Combined	8	15	20

Re-CAG: recurrent coronary angiography; PCI: percutaneous coronary intervention; Re-MI: recurrent myocardial infarction; CABG: coronary artery bypass graft.

DISCUSSION

TRA versus TFA This study demonstrates that the primary PCI using the TRA is feasible. Primary PCI using the TRA resulted in a high procedural success rate (96%) and few complications. However, the TFA was required in 11% of patients, most likely due to detrimental hemodynamics and extensive use of nitroglycerin intravenously during STEMI.[14] In the ACCESS study successful coronary cannulation was achieved in a similar percentage of patients (93%) using the TRA compared with 95.7% and 99.7% for the transbrachial and the TFA groups, respectively.[13] More recent (unpublished) data show higher success rates, increasing with experience.

GP IIb/IIIa blockers GP IIb/IIIa receptor blockage is beneficial in patients undergoing a primary PCI for STEMI, especially in terms of reducing repeat revascularization rates.[5] The recent ADMIRAL Trial demonstrated a reduction in events with abciximab, mainly due to a reduction in events in the first week.[5] Thus far, however, the expected benefit of GP IIb/IIIa receptor blockade with tirofiban for this indication is of unproven, but perceivable benefit.[9,10] In addition, the dose regime for patients undergoing STEMI remains uncertain. The use of a GP IIb/IIIa receptor blocker in combination with primary PCI and stent implantation has also demonstrated improved myocardial salvage rates.[21] Furthermore, it was recently demonstrated that tirofiban infusion improved microperfusion in the setting of primary PCI for STEMI.[22]

Mann et al. showed that with the use of the TRA in acute coronary syndromes, bleeding complications were lower compared to the TFA.[17] The current study showed that the bleeding complications were low despite additional GP IIb/IIIa receptor blockade usage. Bleeding rates with TRA were slightly lower compared to TFA in the ADMIRAL Trial in which 12% of the patients treated with a GP IIb/IIIa receptor blocker experienced minor bleeding (including groin in 6%), and 0.7% experiencedmajor bleeding.[5] In the current trial, 2% of the study population suffered a major bleeding event, and 9% a minor bleeding event; in the TRA group, 1 major vascular access site complication occurred, no major bleeding events, and only 5 (5.6%) minor bleeding complications occurred. It should be noted, however, that we used a different GP IIb/IIIa receptor blocker with a different dose regimen for heparin infusion [10,000 IE bolus followed by 1,000 IE per hour, irrespective of the patient's activated clotting time (ACT) versus ACT-monitored heparin dosing]. In this study, major access site-related bleeding complications were observed in 2 TFA patients (18%).

Early discharge This study demonstrated that the combination of strategies, early revascularization with stenting and use of the TRA under GP IIb/IIIa receptor blockade, allowed early mobilization and early discharge. The inhospital mortality rate after STEMI was low (2%) compared to the Euro Heart Survey (7%).[22] Overall mortality and MACCE at 1 month (4% and 8%) in our group was also low compared to the Euro Heart Survey (1 month 8.4% mortality) and ADMIRAL Trial (in GP IIb/IIIa group 6% mortality at 1 month), but relatively high compared with the CADILLAC Trial's stent plus abciximab group.[5,7,23] At 6 months, the mortality and MACCE rates were 5% and 15%, respectively, and were similar to those of the CADILLAC

(4.2% and 10.2%) and ADMIRAL (mortality 7.4%) results.[5,7] Clinical adverse events remained low throughout the year (mortality 6% and MACCE 20%). It is worth noting that the mean CK-MB peak was 228 IU/L. Early discharge after primary angioplasty (via TFA) is safe for STEMI in low-risk patients.[18,20,24] It should be noted, however, that 31% of the patients in the current study were ≥70 years, the percentage of anterior MIs was high (69%), and 28% of patients had angiographically-confirmed multivessel disease, resulting in higher risk for MACCE. None of our study patients suffered an adverse event within the first week after discharge, indicating that prolonged hospitalization (>4 days) would not result in better patient care in terms of adverse events in this STEMI patient group. Whether early discharge was due to the use of the TRA remains unproven and should be evaluated in a randomized trial. However, reduction of entry site complications with the use of the TRA may well have limited hospital stay. This is supported by the results from the randomized TEMPURA Trial and the large EPIC and EPISTENT trials, in which major bleeding complications were largely attributable to vascular access site complications, consequently resulting in prolonged hospital stays.[12,18,25]

Limitations

A single-center trial has its limitations and biases, and a relatively small population was studied, thus the results should be viewed with caution. However, in demonstrating the feasibility of our approach, it provides valuable information. Tirofiban was chosen although abciximab, at the time of the study's launch, was shown to be more effective. However, the 6-month results of the TARGET Trial demonstrate that despite the fact that a different dosage of tirofiban was used, tirofiban provided a similar level of overall protection compared to abciximab with respect to the composite endpoints of death, MI, and any TVR.[10] Furthermore, we realize that the protocol we used is not fully applicable to every clinic, since our interventional cardiologists are high-volume operators and our personnel and infrastructure are dedicated to the TRA.

CONCLUSION

In summary, the present investigation suggests that the TRA allows early discharge after primary PCI in combination with GP IIb/IIIa receptor blocker treatment and an uncomplicated hospital course, although a larger randomized study is needed to prove efficacy. Current practice. Currently, the majority of our patients undergoing primary PCI for STEMI are treated routinely according to the described protocol in the event of an uncomplicated hospital course. The majority of our patients are treated with the TRA and stent implantation in combination with GP IIb/IIIa receptor blockade followed by discharge within 3 to 4 days. Although early discharge proved to be feasible in this setting, current practice teaches that there is a need for an outpatient clinic visit or an intensive rehabilitation program within the first few weeks after hospital discharge.

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CHAPTER 5

PACLITAXEL-ELUTING VERSUS UNCOATED STENTS IN PRIMARY PERCUTANEOUS CORONARY INTERVENTION

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ABSTRACT

Background Drug-eluting coronary-artery stents have been shown to decrease restenosis and therefore the likelihood that additional procedures will be required after percutaneous coronary intervention (PCI). We evaluated the use of a drug-eluting stent in patients undergoing PCI for acute myocardial infarction with ST-segment elevation.

Methods We randomly assigned 619 patients presenting with an acute myocardial infarction with ST-segment elevation to receive either a paclitaxel-eluting stent or an uncoated stent. The primary end point was a composite of death from cardiac causes, recurrent myocardial infarction, or target-lesion revascularization at 1 year.

Results Baseline clinical and angiographic characteristics in both groups were well matched. There was a trend toward a lower rate of serious adverse events in the paclitaxel-stent group than in the uncoated-stent group (8.8% vs. 12.8%; adjusted relative risk, 0.63; 95% confidence interval, 0.37 to 1.07; *P*=0.09). A nonsignificant trend was also detected in favor of the paclitaxel-stent group, as compared with the uncoated-stent group, in the rate of death from cardiac causes or recurrent myocardial infarction (5.5% vs. 7.2%, *P*=0.40) and in the rate of target-lesion revascularization (5.3% vs. 7.8%, *P*=0.23). The incidence of stent thrombosis during 1 year of follow-up was the same in both groups (1.0%).

Conclusions Although the use of paclitaxel-eluting stents in acute myocardial infarction with ST-segment elevation reduced the incidence of serious adverse cardiac events at 1 year by 4.0 percentage points, as compared with uncoated stents, the difference was not statistically significant. (Current Controlled Trials number, ISRCTN65027270.)

INTRODUCTION

Primary percutaneous coronary intervention (PCI) is now considered the optimal approach to the management of myocardial infarction with ST-segment elevation when the procedure is performed expeditiously and at a high-volume center.[1-5] Stent implantation is associated with an improvement in both early and late outcomes, as compared with balloon angioplasty alone, predominantly as a result of a reduction in target-vessel revascularization.[6,7] Furthermore, drug-eluting stents have been shown to reduce in-stent restenosis (and therefore the need for repeated intervention) in a number of subgroups of patients.[8,9] Retrospective studies and one small, randomized trial have suggested that the use of drug-eluting stents is also beneficial in the setting of primary PCI.[10-13] We aimed to determine whether paclitaxel-eluting stents are superior to uncoated stents in the setting of primary PCI in terms of the rate of serious adverse cardiac events at 1 year.

METHODS

Study design

Our prospective, single-blind, randomized study, called the Paclitaxel-Eluting Stent versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation (PASSION) trial, was performed at two centers in the Netherlands (Onze Lieve Vrouwe Gasthuis in Amsterdam and St. Antonius Hospital in Nieuwegein). The trial was entirely funded by the Department of Interventional Cardiology at Onze Lieve Vrouwe Gasthuis and was approved by the ethics committees at both institutions. All study participants provided oral informed consent, which was documented in the patients' clinical records. This approach to informed consent was explicitly approved by the ethics committee at each center.

Enrollment of patients

We enrolled patients who were between the ages of 18 and 80 years if they had had an acute myocardial infarction with ST-segment elevation (>20 minutes of chest pain and at least 1 mm of ST-segment elevation in at least two contiguous leads or a new left bundle-branch block), reperfusion was expected to be achieved within 6 hours after the onset of symptoms, and the native coronary artery was considered to be suitable for primary PCI with stent implantation. We excluded patients if they had received thrombolytic therapy; the infarction was caused by in-stent thrombosis or restenosis; there was a contraindication to aspirin, clopidogrel, or both; patients were participating in another clinical trial; cardiogenic shock was evident before randomization; the neurologic outcome after resuscitation was uncertain; they had undergone intubation, ventilation, or both; there was known intracranial disease; or the estimated life expectancy was less than 6 months.

Procedures

We administered aspirin (at a dose of 100 to 500 mg) and clopidogrel (300 mg) when patients first arrived at the hospital. A glycoprotein IIb/IIIa receptor blocker was administered at the discretion of the operator. A bolus of 10,000 IU of unfractionated heparin was administered before the procedure.

Coronary angiography was performed through either the radial or the femoral artery. The target segment was filmed in at least two orthogonal planes after the intracoronary administration of 100 to 200 µg of nitroglycerin; quantitative coronary angiography was then performed. The use of thrombectomy devices and predilatation balloons was at the operators' discretion.

As soon as the length and diameter of the stent had been chosen, patients were randomly assigned to receive either a paclitaxel-eluting stent (Taxus Express2, Boston Scientific) or an uncoated stent (Express2 or Liberté, Boston Scientific) in a 1:1 ratio, with the use of permuted blocks of 50. Assignment to study groups was performed with the use of sealed envelopes.

Patients, referring physicians, investigators responsible for obtaining follow-up information, and interventionalists performing repeated procedures were all unaware of treatment assignments.

Stents were deployed with a minimum pressure of 12 atm. If dissection or incomplete coverage of the lesion occurred, additional stents of the same type as the assigned stent were used. Final angiography was performed to obtain views similar to those obtained before the procedure. Epicardial blood flow in the infarct-related artery before and after stent implantation was determined according to the Thrombolysis in Myocardial Infarction (TIMI) classification.[14]

Follow-up

We prescribed 80 to 100 mg of aspirin daily for life and 75 mg of clopidogrel daily for at least 6 months. During each patient's hospital stay, we recorded all adverse events; during follow-up visits at 30 days and at 12 months, we recorded all serious adverse cardiac events (death from cardiac or noncardiac causes, recurrent myocardial infarction, revascularization of the target lesion or target vessel, and coronary-artery bypass grafting [CABG]), as well as interventions to nontarget vessels.

Study end points and definitions

Drs. Laarman and Suttorp adjudicated all end points of the study in a blinded fashion. The primary end point was the first occurrence of a serious adverse cardiac event at 12 months, including death from cardiac causes, recurrent myocardial infarction requiring hospitalization, and ischemia-driven revascularization of a target lesion. The secondary end points of the study were revascularization of a target lesion and a composite of death from cardiac causes or recurrent myocardial infarction.

All deaths were considered to have been from cardiac causes unless a noncardiac cause could be identified. Recurrent myocardial infarction was defined by the development of either pathological Q waves lasting at least 0.4 second in at least two contiguous leads or an increase in the creatine kinase level to more than twice the upper limit of normal with an elevation of the creatine kinase MB isoenzyme. A creatine kinase level of more than five times the upper limit of normal was required for the diagnosis of myocardial infarction after bypass surgery. Patients who still had an elevation in cardiac enzymes received a diagnosis of reinfarction if there was an increase of at least 50% from the previous measurement.

Revascularization of the target lesion was defined as ischemia-driven PCI of the target lesion owing to restenosis or reocclusion within the stent or in the adjacent 5 mm of the distal or proximal segments and included CABG involving the infarct-related artery. Stent thrombosis was defined by the angiographic documentation of either vessel occlusion or thrombus formation within, or adjacent to, the stented segment. Stent thrombosis was categorized as

acute (occurring within 24 hours after the procedure), subacute (occurring 1 to 30 days after the procedure), or late (occurring more than 30 days after the procedure).

Statistical analysis

We calculated that a total of 262 patients would be required in each group, using a two-sided test for differences in independent binomial proportions with an alpha level of 0.05, for the study to have a statistical power of 90% to detect a reduction in the primary end point from an anticipated event rate of 21.7% in the uncoated-stent group to 10.9% in the paclitaxel-stent group, a relative reduction of approximately 50%. This assumption was based on the results of the TAXUS-II trial of the Taxus Express2 paclitaxel-eluting stent.[15] Given the differences in the nature and design of that study and our study (primary vs. elective PCI and no angiographic follow-up), 10% was added to the number of patients. Allowing for attrition, the required study population was determined to be 620 patients.

Baseline data are presented as proportions or mean (±SD) values and were compared with the use of Student's t-test or the Wilcoxon rank-sum test for continuous variables and with Fisher's exact test for categorical variables. A two-sided *P* value of less than 0.05 was considered to indicate statistical significance.

We estimated the cumulative incidence rates of the primary and secondary end points at 1 year with the Kaplan-Meier method.[16] Data on patients who were lost to follow-up were censored at the time of the last contact. Relative risks were calculated by dividing the Kaplan-Meier estimated rate of an event at 1 year in the paclitaxel-stent group by the rate in the uncoated-stent group. The 95% confidence interval (CI) for the relative risk was calculated with the use of the standard errors from the Kaplan-Meier curve. The significance of differences in rates of the end points between treatment groups was assessed by the log-rank test. A Cox proportional-hazards model was used to adjust for baseline variables for calculation of an adjusted relative risk for the primary end point.

RESULTS

Baseline characteristics and procedural results

We screened 1037 patients who had myocardial infarction with ST-segment elevation at the two sites between March 28, 2003, and December 31, 2004. Of these patients, 619 were enrolled in the study; 310 were randomly assigned to the paclitaxel-stent group and 309 to the uncoated-stent group. The most common reasons for exclusion from the trial were an anticipated delay of more than 6 hours between the onset of symptoms and reperfusion, coronary anatomy that was not suitable for stent implantation, cardiogenic shock, and mechanical ventilation. The baseline clinical characteristics of both groups were well matched (Table 1). The mean age was 61 years; 75.9% of the patients were men. The prevalence of diabetes

Table 1. Baseline Clinical Characteristics.*

Characteristics	Paclitaxel-Eluting Stent N = 310	Uncoated Stent N = 309	*P*-value
Age — yr	61±12	61±13	0.91
Male sex — (%)	229 (74)	241 (78)	0.26
Diabetes mellitus — (%)	31 (10)	37 (12)	0.44
Hypertension —(%)	95 (31)	98 (32)	0.80
Hypercholesterolemia —(%)	72 (23)	86 (28)	0.20
Family history of CAD —(%)	125 (40)	110 (36)	0.25
History of smoking cigarettes —(%)	165 (53)	154 (50)	0.42
Previous PCI —(%)	14 (4.5)	13 (4.2)	1.00
Previous stent — (%)	5 (1.6)	6 (1.9)	0.77
Previous CABG — (%)	2 (0.6)	2 (0.6)	1.00
Previous myocardial infarction — (%)	14 (4.5)	18 (5.8)	0.48
Aspirin before PCI — (%)†	219 (71)	199 (64)	0.10
Clopidogrel before PCI — (%)†	118 (38)	109 (35)	0.50
Warfarin — (%)	4 (1.3)	2 (0.6)	0.69
Heparin before PCI — (%)†	67 (22)	54 (18)	0.22
Glycoprotein IIb/IIIa–receptor blocker (abciximab) before PCI — (%)	87 (28)	80 (26)	0.59
Thrombolysis — (%)‡	8 (2.6)	3 (1.0)	0.22
Nitrates before PCI — (%)	67 (22)	67 (22)	1.00
Beta-blockers — (%)	27 (8.7)	31 (10)	0.58
Calcium antagonists — (%)	10 (3.2)	8 (2.6)	0.81
Statins — (%)	25 (8.1)	42 (14)	0.03
Time from onset of chest pain to angioplasty — hr	3.00±1.70	2.97±1.80	0.86
Total ST-segment elevation — mm§	11±8	11±9	0.76

* Plus–minus values are means ±SD. CAD denotes coronary artery disease. † The drug was administered at presentation (before entry into the catheterization laboratory). All patients received aspirin and clopidogrel before PCI; those who had not received these agents before entry into the catheterization laboratory were given them at that time. ‡ A total of 11 patients received a thrombolytic agent before undergoing PCI, which was considered a protocol violation. § This category is the total of measured millimeters of ST-segment elevation in all 12 electrocardiographic leads.

mellitus was low (11.0%). All patients received aspirin and clopidogrel before percutaneous coronary intervention. The time from the onset of symptoms to the first balloon inflation was approximately 3 hours in both groups.

The baseline angiographic characteristics are shown in Table 2. Approximately half the patients had multivessel disease, and in 50.1% of the cases, the left anterior descending coronary artery was the infarct-related artery. TIMI flow grade 2 or 3 was present in 29.3% of patients in the paclitaxel-stent group and in 28.4% in the uncoatedstent group. The majority of patients had an estimated lesion length between 10 mm and 19 mm. The mean reference diameter was 3.13±0.43 mm in the paclitaxel-stent group and 3.20±0.47 mm in the uncoated-stent group.

The procedural characteristics were also well matched (Table 3). The average length of stents was 19 mm in both groups. Glycoprotein IIb/IIIa receptor blockers were used in three

Table 2. Baseline Angiographic Variables.*

Variable	Paclitaxel-Eluting Stent (N = 310)	Uncoated Stent (N = 309)	*P*-value
Coronary artery disease — no. (%)			
1 Vessel	179 (58)	162 (52)	0.20
2 Vessels	82 (27)	100 (32)	0.11
3 Vessels	49 (16)	47 (15)	0.91
Infarct-related artery — no. (%)			
Left main stem	2 (0.6)	0	0.50
Left anterior descending artery	156 (50)	154 (50)	0.94
Right coronary artery	129 (42)	118 (38)	0.41
Left circumflex artery	18 (5.8)	32 (10)	0.04
Intermediate branch	3 (1.0)	4 (1.3)	0.72
Saphenous-vein graft	2 (0.6)	1 (0.3)	1.00
TIMI flow grade — no. (%)			
0	193 (62)	196 (63)	0.80
1	26 (8.4)	25 (8.1)	1.00
2	41 (13)	48 (16)	0.42
3	50 (16)	40 (13)	0.30
Lesion length — no. (%)			
0–9 mm	41 (13)	48 (16)	0.49
10–19 mm	201 (65)	188 (61)	0.36
20–29 mm	50 (16)	52 (17)	0.83
≥30 mm	18 (5.8)	21 (6.8)	0.62
Proximal tortuosity — no. (%)	17 (5.5)	17 (5.5)	1.00
Calcified lesion — no. (%)	28 (9.0)	19 (6.1)	0.22
Thrombus present — no. (%)	213 (69)	204 (66)	0.49
Reference diameter — mm	3.13±0.43	3.20±0.47	0.04
Mean luminal diameter — mm	0.15±0.35	0.17±0.38	0.60
Stenosis — %	95±13	94±15	0.48

* Plus–minus values are means ±SD.

quarters of both groups (abciximab in all cases). TIMI grade 3 flow was established in 93.2% of patients in the paclitaxel-stent group, as compared with 96.1% of patients in the uncoated-stent group. The sizes of infarcts, reflected by the mean peak value of the creatine kinase MB isoenzyme, were similar (193±183 in the paclitaxel-stent group and 210±186 in the uncoated-stent group).

Events during the first 30 days

Events during the first 30 days after the intervention are shown in Table 4 and in Tables 1 through 9 of the Supplementary Appendix (available with the full text of this article at www.nejm.org). No significant differences were found between the two treatment groups. The cumulative incidence of serious adverse cardiac events at 30 days was 4.2% in the paclitaxel-stent group and 6.5% in the uncoated-stent group (*P*=0.21). Acute stent thrombosis (within 24

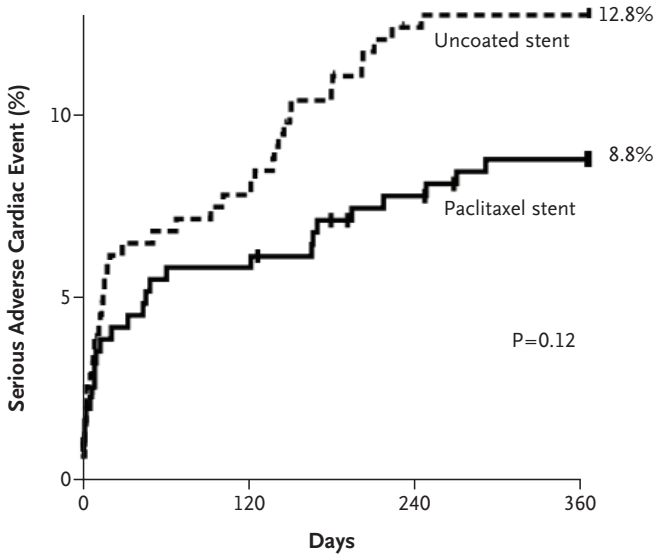
Table 3. Procedural Characteristics.*

Variable	Paclitaxel-Eluting Stent (N = 310)	Uncoated Stent (N = 309)	*P*-value
Stent size — mm	3.21±0.30	3.26±0.38	0.08
Stent length — mm	19±5.6	19±5.5	0.71
No. of stents implanted per patient	1.26±0.55	1.33±0.63	0.14
Maximal balloon inflation pressure — atm	15.84±2.94	15.73±2.94	0.70
Glycoprotein IIb/IIIa–receptor blocker after PCI — (%)	227 (73.2)	230 (74.4)	0.78
Final TIMI flow grade — (%)			
0	2 (0.6)	3 (1.0)	0.69
1	2 (0.6)	2 (0.6)	1.00
2	17 (5.5)	7 (2.3)	0.06
3	289 (93)	297 (96)	0.15
Reference diameter — mm	3.20±0.46	3.24±0.45	0.26
Luminal diameter — mm	3.15±0.47	3.13±0.57	0.66
Residual stenosis — %	3.03±6.6	4.66±12.1	0.04
Procedural success — (%)†	289 (93)	297 (96)	0.15
Maximum creatine kinase — U/liter	2046±2055	2244±2061	0.26
Maximum creatine kinase MB — U/liter	193±183	210±186	0.30

* Plus–minus values are means ±SD.

† Patients in this category had TIMI flow grade 3 and were alive at hospital discharge.

Figure 1. Composite Primary End Point of Death from Cardiac Causes, Recurrent Myocardial Infarction, or Target-Lesion Revascularization at 1 Year. The cumulative incidence of the primary end point of serious adverse cardiac events was 8.8% in the paclitaxel-stent group and 12.8% in the uncoated-stent group (relative risk, 0.69; 95% CI, 0.43 to 1.10; P = 0.12 by the logrank test).



No. at Risk

Uncoated stent	309	282	265	264
Paclitaxel stent	310	290	281	276

hours) occurred in one patient (0.3%) in the paclitaxel-stent group. Subacute stent thrombosis occurred in one patient (0.3%) in the paclitaxel-stent group and in three patients (1.0%) in the uncoated-stent group.

1-Year follow-up

A total of 97.4% of patients in the paclitaxel-stent group and 98.1% of those in the uncoated-stent group underwent complete clinical follow-up. Events during the first year after the intervention are shown in Table 4 and in Tables 10 through 18 of the Supplementary Appendix. The cumulative incidence of the primary end point was 8.8% in the paclitaxel-stent group and 12.8% in the uncoated-stent group (relative risk, 0.69; 95% CI, 0.43 to 1.10; *P*=0.12) (Fig. 1 and Table 4). Multivariate adjustment (which incorporated all the variables in Table 1, Table 2, and Table 3) did not substantially alter the estimate of the relative risk (relative risk, 0.63; 95% CI, 0.37 to 1.07; *P*=0.09). The secondary end points are also shown in Table 4. Although trends were observed in favor of the paclitaxel-stent group, none of these differences were significant.

Table 4. Follow-up at 30 Days and 1 Year.*

Variable	Paclitaxel-Eluting Stent N = 310 (%)	Uncoated Stent N = 309 (%)	*P*-value
Follow-up at 30 days			
Complete data available	308 (99)	306 (99)	
Target-lesion revascularization	7 (2.3)	9 (3.0)	0.60
Recurrent myocardial infarction or death from cardiac causes	10 (3.2)	15 (4.9)	0.31
Composite of major adverse cardiac events	13 (4.2)	20 (6.5)	0.21
Death from any cause	8 (2.6)	13 (4.2)	0.27
Death from cardiac causes	8 (2.6)	13 (4.2)	0.27
Recurrent myocardial infarction	2 (0.7)	5 (1.7)	0.25
Stent thrombosis	2 (0.7)	3 (1.0)	0.65
Repeated PCI of target lesion	2 (0.7)	3 (1.0)	0.65
CABG of target vessel	6 (2.0)	6 (2.0)	0.99
Follow-up at 1 year			
Complete data available	302 (97)	303 (98)	
Target-lesion revascularization	16 (5.3)	23 (7.8)	0.23
Recurrent myocardial infarction or death from cardiac causes	17 (5.5)	22 (7.2)	0.40
Composite of major adverse cardiac events	27 (8.8)	39 (13)	0.12
Death from all causes	14 (4.6)	20 (6.5)	0.30
Death from cardiac causes	12 (3.9)	19 (6.2)	0.20
Recurrent myocardial infarction	5 (1.7)	6 (2.0)	0.74
Stent thrombosis	3 (1.0)	3 (1.0)	0.99
Repeated PCI of target lesion	6 (2.0)	10 (3.4)	0.29
CABG of target vessel	10 (3.3)	15 (5.1)	0.30

* Cumulative incidences were estimated from the Kaplan–Meier curves at 30 days and 1 year and are not simple proportions.

Late stent thrombosis occurred in one patient (0.3%) in the paclitaxel-stent group and in none in the uncoated-stent group, a difference that was not significant. Clopidogrel was used for a median of 9 months (interquartile range, 6 to 12) in both groups; nine patients discontinued clopidogrel prematurely. None of these patients had a thrombotic event. The six patients with stent thrombosis were all compliant with the specified regimen at the time of the event.

DISCUSSION

Our study compared paclitaxel-eluting coronary artery stents with uncoated stents for primary PCI during acute myocardial infarction with ST-segment elevation. The cumulative incidence of the primary end point - a composite of death from cardiac causes, recurrent myocardial infarction, and target-lesion revascularization at 12 months - was 8.8% in the paclitaxel-stent group and 12.8% in the uncoated-stent group. The adjusted risk ratio was 0.63, which was not statistically significant. There was also a trend in favor of the paclitaxel-stent group in the rates of individual adverse events, but no single end point reached statistical significance. In contrast, trials comparing these two types of stents in elective PCI have consistently showed a significant benefit associated with the use of paclitaxel-eluting stents.[8,9]

There are a number of possible explanations for the difference between the results of this trial and those of previous studies. First, the trial power may have been insufficient. Event rates in the uncoated-stent group were much lower than those anticipated in our power calculations. The point estimate of the difference in the primary end point, if accurate, is clinically significant; a larger trial could have demonstrated statistical significance. However, the estimated relative reduction of serious adverse cardiac events by 31% is considerably smaller than that observed in previous trials with drug-eluting stents. This finding has consequences for the cost–benefit profile of these stents for the indication of primary PCI.[8-13] Second, the study design did not include angiographic follow-up. Recurrent stenosis observed during routine follow-up angiography could have led to reintervention without symptoms or objective evidence of ischemia, thus increasing the event rate. In addition, after PCI for myocardial infarction, restenosis may have developed in some patients in the absence of ischemic symptoms, owing either to partial infarction or to a defective warning system. Third, there may have been a difference in response to vascular injury in the setting of primary PCI, as compared with that of more elective procedures. The literature, however, shows that angiographic and clinical restenosis after primary PCI remains an important issue.[6,7] Fourth, the study was performed in patients with relatively large infarct-related arteries in which there was a decreased risk of restenosis. Finally, continuing improvements in the design of stents and the lower thickness of struts may have been responsible for lower rates of restenosis in the uncoated-stent group than in those reported previously.

The results of our study also differ from a series of retrospective analyses and one small, randomized trial evaluating the implantation of drug-eluting stents for myocardial infarction with ST-segment elevation.[10-13] Subgroup analysis of patients undergoing PCI with sirolimus-eluting stents for myocardial infarction in the Thoraxcenter Research Registry showed that the rate of serious adverse cardiac events at 300 days was reduced from 17.0% to 9.4% (*P*=0.02).[11] This pattern was repeated in a retrospective analysis from the Washington Hospital Center using the same stent type.[12] In the Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent vs. Abciximab and Bare-Metal Stent in Myocardial Infarction (STRATEGY) trial involving 175 patients, the rate of death, reinfarction, or target-vessel revascularization at 8 months was reduced from 32% with an uncoated stent to 18% with a sirolimus-eluting stent.[13] These event rates are among the highest reported for any trial of PCI, and the reasons for the high event rates are not entirely clear, although most of the patients in the STRATEGY trial underwent routine follow-up angiography and the mean reference-vessel diameter was considerably smaller than that in our trial. An additional feature of the STRATEGY trial was that by design, a different glycoprotein IIb/IIIa inhibitor was used in the two study groups, which confounded the interpretation of the comparison between the two types of stents.

We did not observe a difference in the rates of stent thrombosis between our two study groups, although the definition of stent thrombosis was conservative (since angiographic documentation was required). Acute or subacute stent thrombosis occurred in two patients (0.6%) in the paclitaxel-stent group and three patients (1.0%) in the uncoated-stent group. This incidence is low, given the thrombotic environment at the time of stent placement, the potential for suboptimal stent deployment in the setting of PCI for acute myocardial infarction, and decreased blood flow in a vessel that supplies infarcted myocardium. In a recent retrospective study from the Thoraxcenter, the incidence of stent thrombosis at 1 month (which was also defined on the basis of angiography) after primary PCI with the use of a paclitaxel-eluting stent was 2.9%.17 We also found no evidence of an increase in the rate of late stent thrombosis, a topic that has recently caused concern.[18]

In this issue of the Journal, a report on the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON) by Spaulding et al.[19] compares sirolimus-eluting stents with uncoated stents in primary PCI among 712 patients. The investigators report a significant difference in the primary end point (the composite of death from cardiac causes, recurrent infarction, and target-vessel revascularization at 1 year) in favor of sirolimus-eluting stents, as compared with uncoated stents (7.3% vs. 14.3%, *P*=0.004). Differences between the two trials - including the type of drug-eluting stent used, the study design (routine follow-up angiography was performed in a subgroup of patients in TYPHOON), primary end points, and inclusion and exclusion criteria - make it difficult to compare the outcomes of our trial with those of TYPHOON. It is worth noting, however, that the event rates in the two groups of patients in TYPHOON are not markedly different from those in our analysis.

CONCLUSION

In conclusion, our study did not show a significant benefit associated with the use of paclitaxel-eluting stents in primary PCI for acute myocardial infarction with ST-segment elevation, as compared with uncoated stents with the same design.

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CHAPTER 6

TWO YEAR FOLLOW-UP AFTER PRIMARY PCI WITH A PACLITAXEL-ELUTING STENT VERSUS A BARE-METAL STENT FOR ACUTE ST-ELEVATION MYOCARDIAL INFARCTION (THE PASSION TRIAL): A FOLLOW-UP STUDY

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ABSTRACT

Aims This follow-up study was performed to assess the long-term effects of paclitaxel-eluting stents (PES) compared with bare-metal stents (BMS) in patients who had undergone a percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI).

Methods and results The PASSION trial randomly assigned 619 patients with STEMI to receive either a PES or BMS. The composite endpoint for the follow-up study was the occurrence of the combination of cardiac death, recurrent myocardial infarction, target lesion revascularisation (TLR) or stent thrombosis at two years. A trend towards a lower rate of the composite endpoint was observed in the PES compared to the BMS group (hazard ratio [HR] 0.70; 95% C.I. 0.45-1.09). This was driven by a reduced TLR in favour of PES (HR 0.60; 95% C.I. 0.34-1.09). Angiographically proven stent thrombosis at two years did not differ significantly between groups (2.1% in the PES group versus 1.4%; HR 1.48; 95% C.I. 0.42-5.23).

Conclusions PES implantation for STEMI did not significantly improve clinical outcome at two years after the index event, although there was a trend towards a lower rate of target-lesion revascularisation. The rate of stent thrombosis did not differ significantly between groups.

INTRODUCTION

Primary percutaneous coronary intervention (PCI) is now considered the optimal approach in the management of ST segment elevation myocardial infarction (STEMI) when the procedure is performed expeditiously and at a high-volume centre.[1-4]Stent implantation is associated with an improvement in both early and late outcomes, as compared with balloon angioplasty alone, predominantly as a result of a reduction in target-vessel revascularisation.[5,6] Drug-eluting coronary artery stents, including paclitaxel-eluting stents (PES), have been shown to improve both early and late outcomes, as compared with bare-metal stents in a variety of clinical settings, predominantly as a result of a reduction in target-vessel revascularisation.[7,8] In contrast, the one year follow-up of the Paclitaxel-Eluting Stent versus conventional Stent in Myocardial Infarction with ST-Segment Elevation (PASSION) trial showed no significant superiority of PES compared to bare-metal stents (BMS) in STEMI, although non-significant trends in favour of PES were found.[9] However, other studies have indicated a significant benefit of sirolimus-eluting stent use in patients with STEMI.[10-11] The current analysis was performed to evaluate whether the differences between the PES and BMS group remained unchanged at two years after stent implantation for STEMI.

In addition, the occurrence of very late stent thrombosis was evaluated. Recently, concern has arisen about the occurrence of serious adverse events caused by stent thrombosis late after drug-eluting stent implantation.[12-15] It has been postulated that delayed endothelialisation and malapposition after drug-eluting stent implantation may lead to late stent thrombo-

sis resulting in myocardial infarction (MI) or death.[16,17] It was recently stated by the FDA panel (November, 2006) that off-label use of drug-eluting stents (i.e. including STEMI) is associated with increased risks of both early and late stent thrombosis. However, the late rates of serious adverse cardiac events after primary PCI for STEMI with drug-eluting stents are unknown. Therefore, we sought to determine whether paclitaxel-eluting stents are safe compared to bare-metal stents in the setting of primary PCI as measured by the rate of serious adverse cardiac events, including the incidence of stent thrombosis, at two years follow-up.

METHODS

Study group

The Paclitaxel-Eluting Stent versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation (PASSION) trial was a prospective, single-blind, randomised study, performed at two centres in the Netherlands (Onze Lieve Vrouwe Gasthuis in Amsterdam and St. Antonius Hospital in Nieuwegein). The study has been registered as an International Randomised Controlled Trial, number ISRCTN65027270. The details of the design and the main results at one year have been published previously.[9] Between March, 2003, and December, 2004, 619 patients were enrolled if they were having an acute myocardial infarction with ST-segment elevation (>20 minutes of chest pain and at least 1 mm of ST-segment elevation in at least two contiguous leads or new left bundle-branch block) and reperfusion was expected to be achieved within six hours from the onset of symptoms. The major exclusion criteria were: cardiogenic shock evident before randomisation; uncertain neurological outcome after resuscitation; mechanical ventilation; or an estimated life expectancy less than six months. This study complied with the principles set out in the Declaration of Helsinki. All study participants provided oral informed consent which was documented in the patients' clinical records. This approach to informed consent was explicitly approved by the authorising ethics committees.

Treatment regimen

Patients were randomly assigned to receive either a paclitaxel-eluting stent (Taxus Express2, Boston Scientific, Natick, MA, USA) or a bare-metal stent (Express2 or Liberté, Boston Scientific, Natick, MA, USA) in a 1:1 ratio using permuted blocks of 50. The assignment to study groups was performed with the use of sealed envelopes. Patients, referring physicians, investigators who were responsible for obtaining follow-up information and the interventionalists performing follow-up procedures were all unaware of treatment assignments. We administered aspirin (100-500 mg) and clopidogrel (300 mg) as soon as patients arrived at the hospital, followed by aspirin 80 to 100 mg daily for life and clopidogrel 75 mg once daily for at least six months.

Angiographic and procedural characteristics

QCA was performed to describe the angiographic profile of the included patient populations. The same QCA system was used in both participating centres and was performed by highly experienced operators familiar with QCA analysis. In the absence of anterograde flow the MLD was estimated as 0 mm and the reference diameter was measured in the angiographically normal looking segment proximal to the occlusion.

Follow-up and outcome

During each patient's hospital stay and follow-up visits at 30 days, one and two years, we recorded all serious adverse cardiac events (death from cardiac or non-cardiac causes, recurrent myocardial infarction, revascularisation of the target lesion or target vessel, and coronary-artery bypass grafting [CABG]), as well as interventions to non-target vessels. Patients were contacted by telephone or by mail. In the event of a repeat hospital admission or any reported adverse event, detailed follow-up information was obtained. If the information could not be checked directly with the patient, it was obtained from the patient's family, family doctor, the insurance company or public records. When patients were lost to follow-up censoring was done at the date of last contact or clinical follow-up. Drs. Laarman and Suttorp adjudicated all endpoints of the study in a blinded fashion. The primary outcome was the first occurrence of a major adverse cardiac event (MACE; including death from cardiac causes, recurrent myocardial infarction, and ischaemia-driven revascularisation of a target lesion) within 24 months. All deaths were considered to be from cardiac causes unless a noncardiac cause could be identified. Recurrent myocardial infarction was defined by the development of either pathological Q waves lasting at least 0.4 second in at least two contiguous leads or an increase in the creatine kinase level to more than twice the upper limit of normal with an elevation of the creatine kinase MB iso-enzyme in combination with symptoms or the need for intervention. Revascularisation of the target lesion was defined as ischaemia-driven PCI of the target lesion if there had been restenosis or reocclusion within the stent or in the adjacent distal or proximal 5 mm and included CABG involving the infarct-related artery. As no routine follow-up angiography was performed, recurrent coronary angiography was performed according to the established clinical guidelines. PCI was then performed if the severity of the lesion was >50% on visual analysis.

A secondary outcome of the study was the occurrence of stent thrombosis. Definition of stent thrombosis in the initial protocol was angiographic confirmation of vessel occlusion or thrombus formation within, or adjacent to, the stented segment. Stent thrombosis was categorised as acute (occurring within 24 hours after the procedure), sub-acute (occurring one to 30 days after the procedure), late (occurring 30 to 365 days after the procedure) or very late (occurring after one year). In addition, the occurrence of stent thrombosis was evaluated according to the Academic Research Consortium (ARC) criteria.[18] Definite or confirmed stent thrombosis: Angiographic confirmation of vessel occlusion or thrombus formation

within, or adjacent to, the stented segment or proven stent thrombosis at autopsy. Probable stent thrombosis: Unexplained death within 30 days or target vessel recurrent MI without angiographic confirmation. Possible stent thrombosis: Unexplained death after 30 days. Stent thromboses following repeated target lesion revascularisation, with or without repeat stent implantation, were also counted.

Statistical analysis

Baseline data are presented as proportions or mean (±SD) values and were compared with the use of Student's t-test or the Wilcoxon rank-sum test for continuous variables and with the Fisher's exact test for categorical variables. A two-sided *P* value of less than 0.05 was considered to indicate statistical significance. We estimated the cumulative incidence rates of the primary and secondary endpoints at two years with the Kaplan-Meier method.[19] Hazards ratios (HR) were calculated with Cox proportional-hazards models with treatment allocation (PES or BMS) as the only covariate. The 95% confidence interval (CI) for the relative risk was calculated with the use of the standard errors from the Kaplan-Meier curve. The significance of differences in rates of the endpoints between treatment groups was assessed by the log-rank test. Statistical analysis was done with the Statistical Package for Social Sciences software (SPSS 13.0 for Windows).

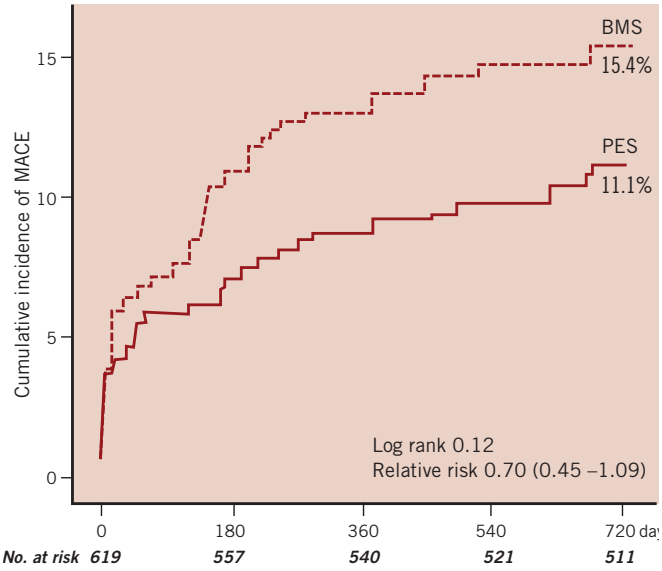
RESULTS

Six-hundred and nineteen patients were enrolled in the study: 310 were randomly assigned to the paclitaxel-stent group and 309 to the bare-metal stent group. The most common reasons for exclusion from the trial were an anticipated delay of more than six hours between the onset of symptoms and reperfusion, coronary anatomy that was not suitable for stent implantation, cardiogenic shock, or mechanical ventilation. The baseline clinical characteristics of both groups were well matched (see Table 1 of Chapter 5). The mean age was 61 years; 76% of the patients were male. Clopidogrel was used for a median of nine months (interquartile range, six to 12).

Angiographic and procedural characteristics

For baseline angiographic and procedural characteristics see Table 2 and 3 of Chapter 5. Approximately half of the patients had multivessel disease, and in 50% of the cases the left anterior descending coronary artery was the infarct-related artery. The majority of patients had an estimated lesion length between 10 mm and 19 mm. The mean reference diameter was 3.13±0.43 mm in the paclitaxel-stent group and 3.20±0.47 mm in the bare-metal stent group. The average length of stents was 19 mm in both groups. TIMI grade 3 flow was established in 93% of patients in the paclitaxel-stent group, as compared with 96% of patients in

Figure 1. Kaplan-Meier survival curves showing the composite endpoint of death from cardiac causes, recurrent myocardial infarction, or target-lesion revascularisation at two years. The cumulative incidence of the primary endpoint of serious adverse cardiac events was 11.1% in the paclitaxel stent (PES) group and 15.4% in the bare-metal stent (BMS) group (relative risk, 0.70; 95% CI, 0.45 to 1.09; P: 0.12 by the logrank test).



the bare-metal stent group (NS). The sizes of infarcts, reflected by the mean peak value of the creatine kinase MB iso-enzyme, were similar (193±183 in the paclitaxel-stent group and 210±186 in the bare-metal stent group).

Incidence of MACE

A total of 96% of patients in the paclitaxel-stent group and 97% of those in the bare-metal stent group underwent complete two year clinical follow-up. Follow-up for death was complete in 98% in both groups. The cumulative incidence of MACE at two years was 11.1% in the paclitaxel-stent group and 15.4% in the bare-metal stent group (HR 0.70; 95% C.I. 0.45-1.09; *P*=0.12) (Figure 1 and Table 1). The cumulative incidence of cardiac death, recurrent MI or stent thrombosis was 8.5% in both groups (HR 0.95; 95% C.I. 0.56-1.63; *P*=0.86). Figure 2 shows the incidence of target lesion revascularisation up to two years of follow-up.

Stent thrombosis

The cumulative incidence of angiographically proven stent thrombosis was similar between the two treatment groups, 2.1% (n=6) in the paclitaxel-stent group versus 1.4% (n=4) in the bare-metal stent group. Acute stent thrombosis (within 24 hours) occurred in one patient (0.3%) in the paclitaxel-stent group. Sub-acute stent thrombosis occurred in one patient (0.3%) in the paclitaxel-stent group and in three patients (1.0%) in the bare-metal stent group. Very-late stent thrombosis occurred in three patients (1.0%) in the paclitaxel-stent group and

Table 1. Two year follow-up.

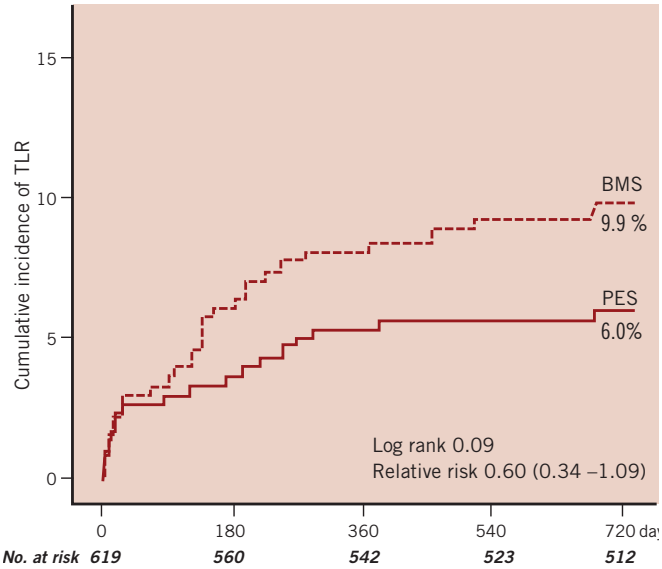
Events	Paclitaxel-Eluting Stent N (%)	Uncoated Stent N (%)	HR (95% C.I.)	Log Rank *P*-value
N	303 (98)	303 (98)		
Death by all causes	21 (6.9)	27 (8.8)	0.77 (0.43-1.36)	0.36
Cardiac death	17 (5.6)	22 (7.2)	0.76 (0.41-1.44)	0.40
	Paclitaxel-Eluting Stent N (%)	**Uncoated Stent N (%)**	**HR (95% C.I.)**	**Log Rank *P*-value**
N	298 (96)	299 (97)		
Recurrent MI	9 (3.1)	7 (2.4)	1.27 (0.47-3.40)	0.64
ST or recurrent MI	9 (3.1)	7 (2.4)	1.27 (0.47-3.40)	0.64
ST or cardiac death	23 (7.6)	25 (8.2)	0.91 (0.52-1.60)	0.74
ST or Re-MI or cardiac death	26 (8.5)	26 (8.5)	0.99 (0.57-1.70)	0.97
Repeat PCI of target lesion	8 (2.7)	15 (5.2)	0.52 (0.22-1.22)	0.13
CABG of target vessel	10 (3.3)	18 (6.1)	0.55 (0.25-1.18)	0.12
TLR (PCI + CABG)	18 (6.0)	29 (9.9)	0.60 (0.34-1.09)	0.09
MACE	34 (11)	47 (15)	0.70 (0.45-1.09)	0.12
ARC definite	6 (2.1)	4 (1.4)	1.48 (0.42-5.23)	0.54
ARC probable	2 (0.7)	4 (1.3)	0.49 (0.09-2.68)	0.40
ARC possible	9 (3.1)	6 (2.1)	1.47 (0.52-4.14)	0.46
ARC cumulative	17 (5.8)	14 (4.7)	1.19 (0.59-2.42)	0.76
	Paclitaxel-Eluting Stent N (%)	**Uncoated Stent N (%)**	**HR (95% C.I.)**	**Log Rank *P*-value**
N	298 (96)	299 (97)		
Acute stent thrombosis (< 24 hours)	1 (0.3)	0		
Sub-acute stent thrombosis (> 24 hours < 30 days)	1 (0.3)	3 (1.0)		
Late stent thrombosis (> 30 days < 1 year)	1 (0.3)	0		
Very late stent thrombosis (> 1 year)	3 (1.0)	1 (0.3)		
Total	6 (2.1)	4 (1.4)	1.48 (0.42-5.23)	0.54

Cumulative incidences were estimated from the Kaplan-Meier curves at two year and are not simple proportions. ARC: Academic Research Consortium; CABG: coronary artery bypass grafting; MACE: major adverse cardiac event; MI: myocardial infarction; PCI: percutaneous coronary intervention; TLR: target lesion revascularisation

in one (0.3%) in the bare-metal stent group. These four patients with stent thrombosis beyond one year were all compliant with the use of aspirin at the time of the event and there were no specific confounding factors involved. One of the patients in the PES group had a very late stent thrombosis in the PES that was implanted in a lesion adjacent to the initial stent six months after the index event.

The occurrences of stent thrombosis according to the ARC criteria are shown in Table 1. The cumulative incidences of definite, probable or possible stent thrombosis were 5.8% in the PES group versus 5.1% in the BMS group (HR 1.19; 95% C.I. 0.59-2.42; *P*=0.62).

Figure 2. Kaplan-Meier survival curves showing cumulative incidence of target lesion revascularisation (TLR) at two years. The cumulative incidence of TLR was 6.0% in the paclitaxel-stent (PES) group and 9.9% in the bare-metal stent (BMS) group (relative risk, 0.60; 95% CI, 0.34 to 1.09; P: 0.09 by the logrank test).



DISCUSSION

This is the first randomised study to report clinical outcome with late follow-up two years after PES or BMS implantation for STEMI. The additional information pertaining to two year follow-up is important, as currently the information available on drug-eluting stents post STEMI is almost exclusively limited to one year of follow-up, a duration too short to fully appreciate the risks and/or benefits of drug-eluting stents, particularly as late stent thrombosis beyond one year seems to be of particular concern with drug-eluting stents. In our study, the use of a paclitaxel-eluting stent was not superior to that of a bare-metal stent in patients undergoing a primary PCI for STEMI, apart from a trend towards less target-lesion revascularisation in the PES group. The cumulative incidence of the primary endpoint - a composite of cardiac death, recurrent myocardial infarction, and target-lesion revascularisation at 24 months - was 11.1% in the PES group and 15.4% in the BMS group. The relative risk of 0.70 (95% C.I. 0.45-1.09) was similar to that observed at one year (0.69; 95% C.I. 0.43-1.10) and was not statistically significant.[9] The rates of individual adverse events were similar in both groups, except for target lesion revascularisation that was in favour of the PES group, however this did not reach statistical significance. These results are in contrast to other trials with prolonged follow-up comparing the use of a PES with a BMS. Previous trials observed improved outcome with the use of PES in

a number of clinical conditions (except for STEMI).[7,8] As discussed previously,[9] several factors may account for the discrepancies between our results and those reported for PES in other clinical settings. In summary, the event rates in the BMS group were much lower than those anticipated in our power calculations, possibly due to improvements in stent design and/or implantation techniques. This TLR rate was noticeably lower compared to the TLR rates after BMS implantation observed in all other randomised trials with sirolimus- and paclitaxel-eluting stents in STEMI.[10,20] Secondly, the study design did not include angiographic follow-up in contrast to the majority of these previous trials. Third, there may be a difference in the response to vascular and myocardial injury after PCI for myocardial infarction, when compared with the response in more elective procedures. Importantly, the relative risks and non-significant trends were similar to those seen at one-year follow-up and we did not see a late 'catch-up' phenomenon with the use of PES after longer follow-up.

Whereas restenosis is considered a relatively benign adverse event, stent thrombosis may be fatal in up to 45%.[21] Although this study was not powered to detect a difference in stent thrombosis, it is notable that the current study showed an equal safety profile for both stents at two years after implantation in patients with STEMI. There was no significant increase of catastrophic adverse events associated with the use of a PES. The cumulative endpoint of cardiac death, recurrent MI or stent thrombosis was similar in both groups, with a relative risk of 0.95. Although angiographically proven very late stent thrombosis was higher in the PES group (1.0%) compared to the BMS group (0.3%), the cumulative incidences of definite, probable or possible stent thrombosis (according to the ARC criteria) did not show an increase after PES implantation. However, these rates of stent thrombosis must be read with caution given the limited size of the study population evaluated for the occurrence of stent thrombosis. Much larger numbers of patients are needed to prove statistical and clinical significance. In the current analysis we used a conservative definition of stent thrombosis - angiographically proven - and less conservative definitions of stent thrombosis - according to the ARC, including stent thrombosis after repeat revascularisation.

Regardless of the definition, the incidence of stent thrombosis, according to the ARC criteria, was low in both treatment groups, especially given the complex conditions of unstable patients during acute myocardial infarction, with a thrombotic environment at the time of stent placement, augmented platelet activation,[22] the potential for suboptimal stent deployment, and decreased blood flow in the infarct-related artery. Therefore, the current analysis of patients two years after PES implantation suggests that the "offlabel" use of PES in primary PCI for STEMI shows an equal safety profile compared to BMS. These results are in line with recently published meta-analyses of randomised trials that had long-term follow-up after drug-eluting stent implantation showing no increase in the rates of stent thrombosis with the use of drug-eluting stents.[23,24] However, our results differ from previously reported studies that suggest that drug-eluting stent implantation may be associated with an increase of stent

thrombosis and death.[12-15] It should be noted that none of these studies were performed in a randomised manner in patients with STEMI.

In our study, all patients were expected to have discontinued the use of clopidogrel at one year after the index procedure. Although there was an increase of events in the PES group compared with the BMS group after one year, this was not statistically significant. Currently, all patients are advised to use clopidogrel for one year after drug-eluting stent implantation and the impact of this prolonged strategy on outcome is not yet known. Early discontinuation of anti-platelet therapy may be associated with an increased risk of thrombosis, but the optimal duration of clopidogrel remains undefined. This increase of events should be evaluated with longer follow-up in larger randomised trials.

Taken together, the mandatory use of PES in acute MI remains debatable. Additionally the use of drug-eluting stents may not be necessary for STEMI in view of the predominantly large sizes of culprit vessels that have a low expected risk of restenosis (TLR 9.9% in the BMS group). However, it is necessary to wait for the longer follow-up of larger randomised trials, meta-analyses and substudies on the use of drug-eluting stents for acute MI as the literature shows that angiographic and clinical restenosis after primary PCI remains an important issue.[4,5]

Study limitations

A limitation of this study lies in the fact that the power calculations were not based on the hypothesis of the current analysis; e.g., the current study was not powered to detect differences in stent thrombosis or death: therefore these data remain observational. Larger studies with longer follow-up periods and larger patient numbers are required to definitively answer the question of whether the use of drug-eluting stents in primary PCI would improve or decrease survival after acute MI. A further limitation is the lack of an independent clinical event committee, as all events were adjudicated in a blinded fashion by two interventional cardiologists.

CONCLUSION

In conclusion, the PASSION study did not show any significant clinical benefit associated with the use of paclitaxel-eluting stents as compared with the use of bare-metal stents of same design. In addition, there was no significant increase of stent thrombosis after PES implantation in primary PCI at two years after stent implantation and one year after discontinuation of clopidogrel.

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CHAPTER 7

META-ANALYSIS OF RANDOMISED TRIALS ON DRUG-ELUTING STENTS VERSUS BARE METAL STENTS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Aims To compare the efficacy and safety of drug-eluting stents versus bare-metal stents in patients with acute ST-segment elevation myocardial infarction.

Methods and results We performed a meta-analysis of 8 randomised trials comparing drug-eluting stents (sirolimus-eluting or paclitaxel-eluting stents) with bare-metal stents in 2.786 patients with acute ST-segment elevation myocardial infarction. All patients were followed up for a mean of 12.0 to 24.2 months. Individual data were available for 7 trials with 2476 patients. The primary efficacy end point was the need for reintervention (target lesion revascularisation). The primary safety end point was stent thrombosis. Other outcomes of interest were death and recurrent myocardial infarction. Drug-eluting stents significantly reduced the risk of reintervention, hazard ratio of 0.38 (95% confidence interval: 0.29 to 0.50), $P<0.001$. The overall risk of stent thrombosis: hazard ratio of 0.80 (0.46 to 1.39), $P=0.43$; death: hazard ratio of 0.76 (0.53 to 1.10), $P=0.14$; and recurrent myocardial infarction: hazard ratio of 0.72 (0.48 to 1.08, $P=0.11$) were not significantly different for patients receiving drug-eluting stents versus bare-metal stents.

Conclusion The use of drug-eluting stents in patients with acute ST-segment elevation myocardial infarction is safe and improves clinical outcomes by reducing the risk of reintervention compared with bare-metal stents.

INTRODUCTION

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy for patients presenting with acute myocardial infarction with ST-segment elevation.[1,2] As compared with balloon angioplasty, routine implantation of bare metal stents has been associated with improved clinical outcome mainly due to the decreased risk for reintervention.[3,4] Nevertheless, restenosis remains an important limitation of the use of bare-metal stents in patients with acute myocardial infarction.[4-7]

Drug-eluting stents effectively reduce restenosis while maintaining a good safety profile in many lesion and patients groups.[8,9] However, concerns have been raised with regard to the safety of drug-eluting stents in patients with acute myocardial infarction.[10] Data from registry studies have suggested that implantation of drug-eluting stents during primary PCI could be associated with an increased risk for stent thrombosis, which is associated with high morbidity and mortality rates.[11,12] Recently, the results of several randomised trials of drug-eluting stents in patients undergoing primary PCI for acute ST-segment elevation myocardial infarction have been reported. These studies had, however, insufficient power to assess the risk of rare adverse events. Furthermore, they did not consistently show the superior effectiveness of drug-eluting stents in that particular setting.[13-15] Meta-analyses of randomised trials have the

potential to increase power and improve precision of treatment effects.[16] A meta-analysis has recently been published including 7 randomised trials with a total number of 2.357 patients.[17] However, this meta-analysis was based on summary data exctracted from meeting abstracts in 4 of the 7 trials.[17] Toma et al.[18] suggest caution in the use of these data due to common discrepancies in results between meeting abstracts and subsequent full-length publications. A meta-analysis based on individual patient data yields much more accurate results and is the "gold standard" to perform time-to-event analyses.[19]

We performed a meta-analysis predominantly based on individual patient data from randomised trials comparing drug-eluting stents with bare metal stents to evaluate the efficacy and safety of drug-eluting stents in patients with acute ST-segment elevation myocardial infarction.

METHODS

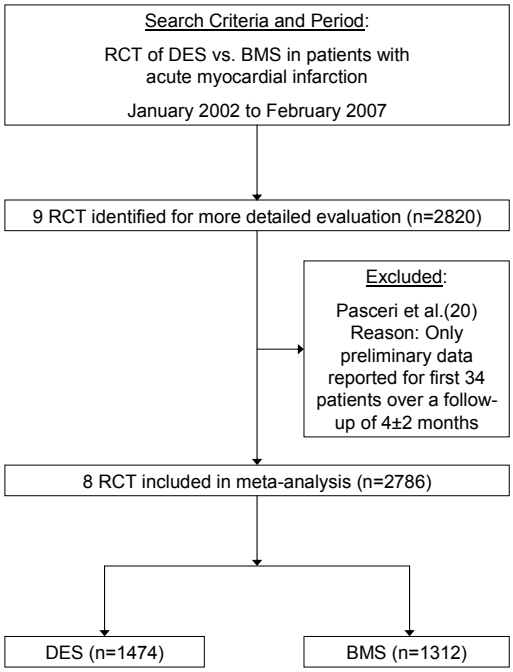
Literature search

We performed an electronic search of the United States National Library of Medicine (PubMed, at www.pubmed.gov), the United States National Institutes of Health clinical trials registry (www.clinicaltrials.gov), and the Cochrane Central Register of Controlled Trials (http://www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html). The key words used included: ´myocardial infarction´, ´primary´, ´angioplasty´, ´PCI´, ´ST-segment elevation´, ´drug-eluting stent´, ´sirolimus-eluting stent´, ´paclitaxel-eluting stent´, ´clinical trial´, ´randomized´. Internet-based sources of information on the results of clinical trials in cardiology (www.theheart.org, www.cardiosource.com/clinicaltrials, www.clinicaltrialresults.com, and www.tctmd.com) were also searched. Additional data sources included conference proceedings from the American College of Cardiology, American Heart Association, and European Society of Cardiology meetings. We also identified relevant reviews and editorials from major medical journals published within the last year and assessed for possible information on trials of interest. The search period was between January 2002 and February 2007.

Study selection

To be selected for this meta-analysis, studies comparing drug-eluting stents with bare metal stents in patients undergoing primary PCI of ST-segment elevation acute myocardial infarction had be randomised and had their results reported or made available by the trial investigators for a mean follow-up period of at least 12 months. Articles were searched and reviewed independently by two of the authors (A.D. and J.M.); those meeting the inclusion criteria were selected for further analysis. A total of 9 trials were identified. The trial of Pasceri et al.[20] was excluded because it only reported preliminary data of the first 34 patients over a follow-up of 4±2 months. Finally, 8 trials were included in this meta-analysis (Figure 1).[13-15,21-25]

Figure 1. Flowchart of selected studies. BMS, bare-metal stent; DES, drug-eluting stent; RCT, randomized control trial.



Study outcomes and data collection

The primary efficacy end point of this meta-analysis was the need of reintervention (target lesion revascularisation). The primary safety end point of this meta-analysis was stent thrombosis. Secondary end points were death and recurrent myocardial infarction. The composite of death, recurrent myocardial infarction or reintervention was also assessed. The event definitions used in individual trials are displayed in the Table 1. The adjudication of events in each trial was performed by the same event committee over the entire follow-up period. Survival was calculated from the date of randomisation to the date of death. Data for surviving patients were censored on the date of last follow-up.

An electronic form containing the data fields to be completed for individual patients was sent to all principal investigators of the trials. Individual patient data could be obtained for 7 trials.[13-15,21-24]

The data requested for each enrolled patient included the date of randomisation, allocated treatment, diabetes status, event status (including death, myocardial infarction, coronary reintervention [percutaneous or surgical], stent thrombosis and their respective dates of occurrence) and date of last follow-up. All data were thoroughly checked for consistency (logical checking and checking against the original publications). Any queries were resolved and the final database entries verified by the responsible trial investigator.

Each trial was evaluated for the adequacy of allocation concealment, performance of the analysis according to the intention-to-treat principle, and blind assessment of the outcomes of interest. We used the criteria recommended by Altman et al.[26] and Jüni et al.[27] to assess the adequacy of allocation concealment. In 2 trials, a modified intention-to-treat principle, i.e. exclusion of patients who did not receive the study stent, was used.[14,25]

Statistical methods

We performed survival analyses using the Mantel-Cox method stratified by trial. The log-rank test was used to calculate hazard ratios and their 95% confidence intervals.

Trials in which the event of interest was not observed in either treatment group were discarded from the analysis of that event. In case only one of the groups of an individual trial had no event of interest, the treatment effect estimate and its standard error were calculated after adding 0.5 to each cell of the 2x2 table for that trial.[28]

We used the Cochran-test to assess heterogeneity across trials. We also calculated the I^2 statistic to measure the consistency between trials with values of 25%, 50%, and 75% showing respectively, low, moderate and high heterogeneity.[29] Hazard ratios from individual trials were pooled using the DerSimonian and Laird method for random effects.[30]

We performed sensitivity analyses by comparing the treatment effects obtained with each trial removed consecutively from the analysis with the overall treatment effects. Results were considered statistically significant at two-sided $P<0.05$. Statistical analysis was performed by using the Stata software, version 9.2 (Stata Corp, College Station, Tex). Survival curves are presented as simple, non-stratified Kaplan-Meier curves across all trials and constructed with the use of S-Plus software version 4.5. (Insightful Corporation, Seattle, WA).

RESULTS

Eight trials with 2.786 patients were included in this meta-analysis. The main characteristics of these trials are summarised in Table 2. The mean age of participants in individual trials varied from 59.2 years to 64.0 years. Drug-eluting stents consisted of paclitaxel-eluting stents in 2 of the trials and sirolimus-eluting stents in 4 other trials; in the remaining 2 trials, a 3-arm design was used including both paclitaxel-eluting and sirolimus-eluting stents.[21,22] The recommended length of postprocedural thienopyridine therapy was 3[15], 6[13,14,21,22] or 12 months.[23-25] The mean length of follow-up ranged from 12.0 to 24.2 months. Patient-level data were available for 7 trials with 2476 patients.[13-15,21-24]

Figure 2A shows the absolute numbers of patients who experienced the primary efficacy end point of reintervention in each trial by treatment group, with the hazard ratio for each trial. Overall, use of drug-eluting stents was associated with a hazard ratio for reintervention of 0.38 (95% confidence interval: 0.29 to 0.50), $P<0.001$, compared with use of the bare

Table 1. End Point Definitions in Each Trial

Study	Death	Recurrent MI	Reintervention	Stent Thrombosis
BASKET-AMI[22]	Cardiac, if clearly due to a cardiac event, otherwise noncardiac	Typical chest pain with typical rise (and fall) of cardiac enzymes or new Q-waves/ST-T wave changes on ECG	PCI or CABG driven by a lesion in the same epicardial vessel as initially treated	Angiographic evidence in the presence of an ischemic clinical event
Di Lorenzo[21]	Cardiac, unless a noncardiac cause could be identified	Recurrence of anginal symptoms with typical ECG changes and increase of CK-MB or troponin	Any CABG or PCI of the target vessel in the presence of symptoms or signs of ischemia	Angiographically documented thrombus within the stent associated to typical chest pain and ST-segment modification with or without a significant rise of enzymes
HAAMU-STENT[23]	Cardiac, if sudden unexpected death or witnessed fatal arrhythmia or cardiac failure	Clinical picture of myocardial infarction with ST-segment changes and elevated cardiac markers or angiographic stent thrombosis	Any CABG of the target vessel or a PCI due to angiographic restenosis in the presence of symptoms or signs of ischemia	Acute ST-segment elevation myocardial infarction plus angiographic thrombus
MISSION*[25]	Cardiac, unless a noncardiac cause could be identified	Development of new Q-waves on ECG or a troponin-T rise above normal (>25% above previous value) with symptoms or need for reintervention	Any CABG or PCI of the target vessel	Angiographically documented thrombus within the stent and/or typical chest pain with recurrent ST-segment elevation in combination with a significant rise of troponin levels and/or the presence of new Q-waves
PASSION[13]	Cardiac, unless a noncardiac cause could be identified	Q waves on ECG or an increase in the CK level ≥2 times the ULN or 50% higher than the previous value with symptoms or need for reintervention	Any CABG of the target vessel or a PCI due to angiographic restenosis in the presence of symptoms or signs of ischemia	Angiographic documentation of either vessel occlusion or thrombus formation within, or adjacent to, the stented segment
SESAMI[24]	Cardiac, unless an unequivocal noncardiac cause could be established	Recurrent ischemic symptoms or ECG changes accompanied by an increase in cardiac enzymes ≥2 times the ULN or 50% higher than the previous value	Any CABG of the target vessel or a PCI due to angiographic restenosis in the presence of symptoms or signs of ischemia	Angiographic evidence in the presence of an acute coronary syndrome
STRATEGY[15]	Cardiac, unless an unequivocal noncardiac cause could be established	Recurrent ischemic symptoms or ECG changes accompanied by an increase in cardiac enzymes above the normal limit or 50% higher than the previous value	Any CABG or PCI of the target vessel in the presence of symptoms or signs of ischemia	Angiographic evidence in the presence of clinical symptoms or ECG changes suggestive of acute ischemia

Table 1. End Point Definitions in Each Trial

Study	Death	Recurrent MI	Reintervention	Stent Thrombosis
TYPHOON[a][14]	Cardiac, if a cardiac cause cannot be excluded	Recurrence of clinical symptoms or the occurrence of ECG changes accompanied by new elevation of cardiac enzymes (1.5 times the previous value or 3 times the ULN)	Any CABG of the target vessel or a PCI due to angiographic restenosis in the presence of symptoms or signs of ischemia, or only due to severe restenosis (≥70% diameter stenosis)	Acute and subacute stent thrombosis were defined as angiographic proof of vessel occlusion, any recurrent Q-wave MI in the territory of the stented vessel, or any death from cardiac causes. Late stent thrombosis was defined as any recurrent MI with angiographic proof of vessel occlusion[b]

CABG, aorto-coronary bypass surgery; PCI, percutaneous coronary intervention; HAAMU-STENT, The Helsinki area acute myocardial infarction-treatment re-evaluation—should the patient get a drug-eluting or a normal stent trial; MISSION, a prospective randomized controlled trial to evaluate the efficacy of drug-eluting stents vs. bare-metal stents for the treatment of acute myocardial infarction; PASSION, the paclitaxel-eluting stent vs. conventional stent in myocardial infarction with ST-segment elevation trial; SESAMI, the randomized trial of sirolimus stent vs. bare stent in acute myocardial infarction trial; STRATEGY, the single high-dose bolus Tirofiban and sirolimus eluting stent vs. Abciximab and bare-metal stent in myocardial infarction trial; TYPHOON, the trial to assess the use of the Cypher stent in acute myocardial infarction treated with balloon angioplasty.

[a]A 'modified intention-to-treat' principle was adopted in the trial, i.e. a randomized patient was included in the analysis only if he received stent(s).

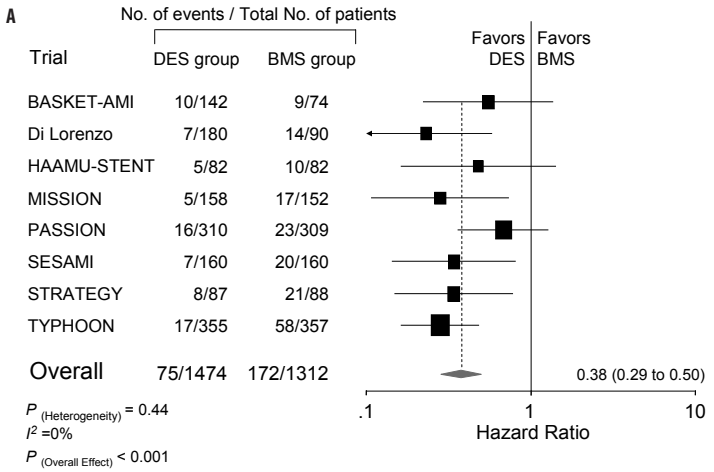
[b]According to protocol, patients undergoing reintervention had to be censored from further assessment of stent thrombosis.

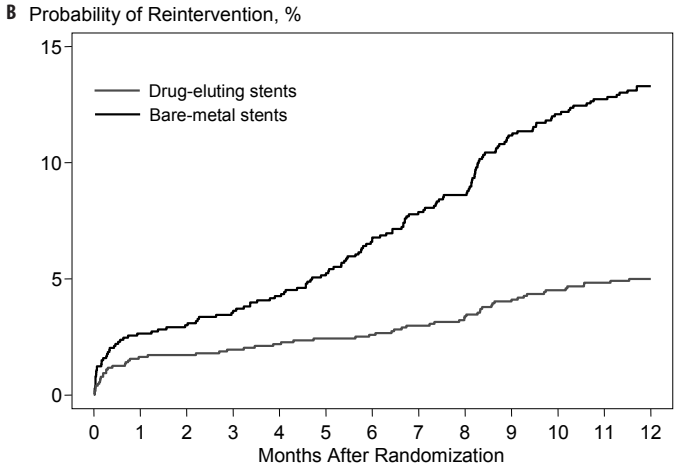
Table 2. Main Characteristics of the Trials

Study	N	Age	Type of DES	Individual Patient Data Available	Primary End Point	Thienopyridine Therapy (months)	Mean Follow-Up (months)
BASKET-AMI[22]	216	62	PES and SES	Yes	Cardiac death, MI, or reintervention	6	18.0
Di Lorenzo[21]	270	64	PES and SES	Yes	Death, MI, or reintervention	6	12.0
HAAMU-STENT[23]	164	63	PES	Yes	Angiographic late lumen loss	12	16.7
MISSION[25]	310	59	SES	No	Angiographic late lumen loss	12	12.0
PASSION[13]	619	61	PES	Yes	Cardiac death, MI, or reintervention	6	12.0
SESAMI[24]	320	62	SES	Yes	Angiographic binary restenosis	12	12.3
STRATEGY[15]	175	63	SES	Yes	Death, MI, stroke, or angiographic binary restenosis	3	24.2
TYPHOON[14]	712	59	SES	Yes	Cardiac death, MI, or reintervention	6	12.1

DES - drug-eluting stent,; PES - paclitaxel-eluting stent; SES - sirolimus-eluting stent; MI - myocardial infarction; BASKET-AMI - Basel Stent Kosten Effektivitäts in Acute Myocardial Infarction trial; HAAMU-STENT - The Helsinki area acute myocardial infarction-treatment re-evaluation - Should the patient get a drug-eluting or a normal stent trial; MISSION - A Prospective Randomized Controlled Trial to Evaluate the Efficacy of Drug-Eluting Stents versus Bare-Metal Stents for the Treatment of Acute Myocardial Infarction; PASSION - the Paclitaxel-Eluting Stent versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation trial; SESAMI - the Randomized Trial of Sirolimus Stent vs. Bare Stent in Acute Myocardial Infarction trial; STRATEGY - the Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent vs. Abciximab and Bare Metal Stent in Myocardial Infarction trial; TYPHOON - the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty.

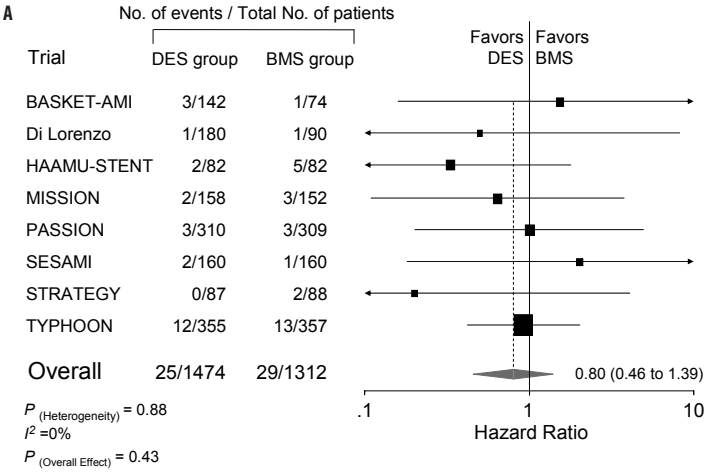
Figure 2. (A) Absolute numbers of patients requiring reintervention and hazard ratios for this endpoint with drug-eluting stents vs. bare-metal stents for individual trials and the pooled population. Hazard ratios are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log hazard ratio. DES, drug-eluting stent; BMS, bare-metal stent. (B) Kaplan–Meier curves of reintervention in each of the stent groups for the pooled population.

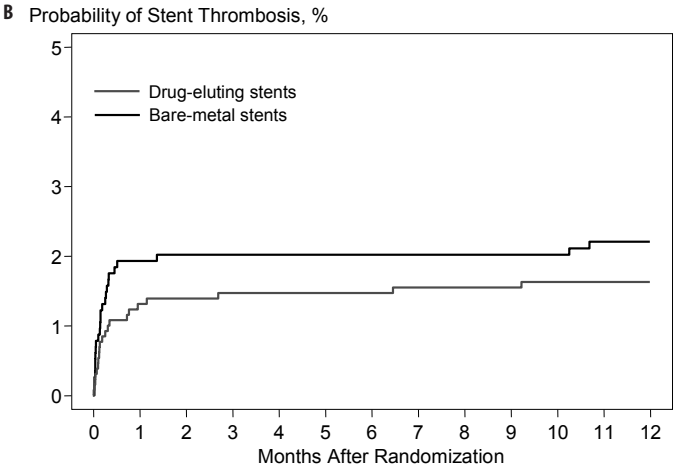




metal stent. There was no heterogeneity across trials (I^2=0%) and no significant interaction (P=0.07) between treatment effect and type of drug-eluting stent (sirolimus-eluting stent or paclitaxel-eluting stent) used. Sequential exclusion of each individual trial from the analysis of the primary endpoint yielded hazard ratios ranging from 0.33 (0.24 to 0.45) to 0.42 (0.30 to 0.57), which were not significantly different from the overall hazard ratio. Specifically, the hazard ratio for reintervention associated with the use of drug-eluting stents was 0.39 (0.29 to 0.53) when the trial for which no individual patient data were available was excluded.[25] Figure 2B shows one-year probability curves for reintervention in the 2 treatment arms. An early and

Figure 3. (A) Absolute numbers of patients with stent thrombosis and hazard ratios for stent thrombosis associated with drug-eluting stents vs. bare-metal stents for individual trials and the pooled population. Hazard ratios are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log hazard ratio. DES, drug-eluting stent; BMS, bare-metal stent. (B) Kaplan–Meier curves of stent thrombosis in the pooled population according to stent type.

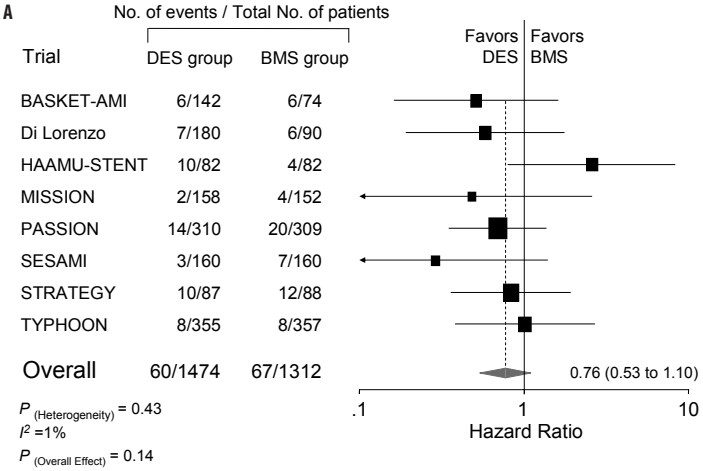


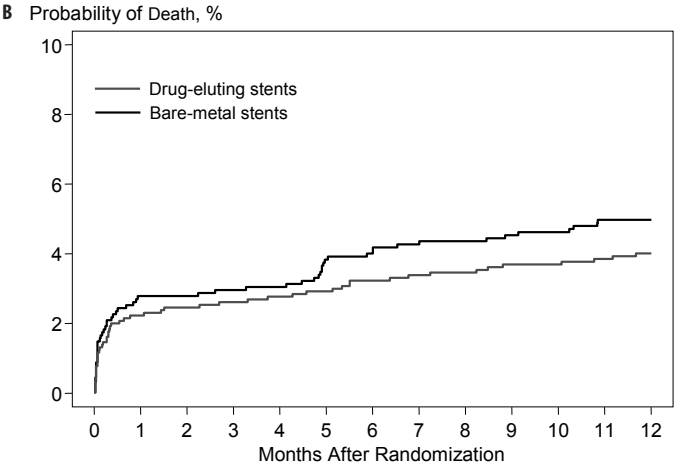


continuous separation of the curves is readily visible. The probability of reintervention was 5.0% in the drug-eluting stent group and 13.3% in the bare-metal stent group.

Figure 3A shows the number of patients who suffered the primary safety end point of stent thrombosis (as defined in the individual trials). The hazard ratio for stent thrombosis was 0.80 (0.46 to 1.39), *P*=0.43. There was no heterogeneity across trials (I^2=0%) and no significant interaction (*P*=0.89) between treatment effect and type of drug-eluting stent used (sirolimus-eluting stent or paclitaxel-eluting stent). In addition, the hazard ratio for stent thrombosis associated with the use of drug-eluting stents was 0.82 (0.46 to 1.47) when the trial for which

Figure 4. (A) Absolute numbers of patients experiencing death and hazard ratios for death associated with drug-eluting stents vs. bare-metal stents for individual trials and the pooled population. Hazard ratios are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log hazard ratio. DES, drug-eluting stent; BMS, bare-metal stent. (B) Kaplan–Meier curves of mortality in each of the stent groups for the pooled population.



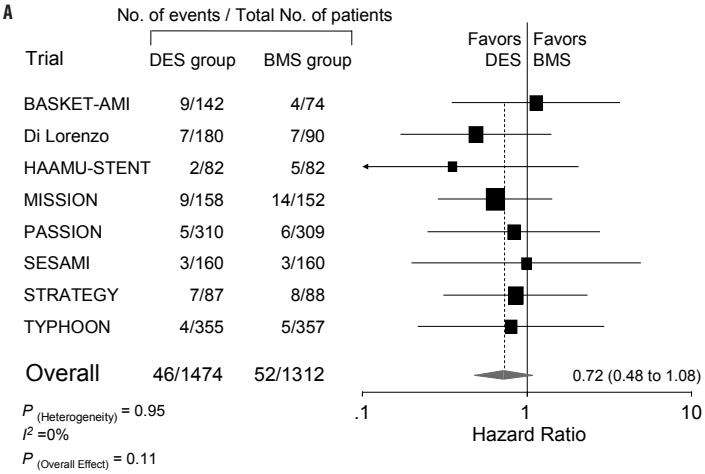


no individual patient data were available was excluded.[25] Figure 3B shows one-year curves of stent thrombosis probability for the 2 treatment groups. The probability of stent thrombosis was 1.6% in the drug-eluting stent group and 2.2% in the bare-metal stent group. Three stent thromboses occurred after 1 year: two in the drug-eluting stent group and one in the bare-metal stent group.

Figure 4A shows the absolute numbers of deaths in each trial by treatment group with the hazard ratio for each trial. There was no heterogeneity across the trials (I^2=1%) and no significant interaction (P=0.48) between treatment effect and type of drug-eluting stent used.

Overall, use of the drug-eluting stent was associated with a hazard ratio for death of 0.76 (0.53 to 1.10), *P*=0.14, compared with use of the bare metal stent. Ninety-eight of the 121 death cases (81.0%) observed in the 7 trials for which patient-level data were available were of cardiac origin, without any significant difference between the drug-eluting stent group (45 of 58 cases) and bare-metal stent group (53 of 63 cases), *P*=0.36. Figure 4B shows one-year mortality curves for the 2 treatment groups. The probability of death was 4.0% in the drug-eluting stent group and 5.0% in the bare-metal stent group. Twelve patients died after 1 year: 6 in the drug-eluting stent group and 6 in the bare-metal stent group.

Figure 5. (A) Absolute numbers of patients experiencing recurrent myocardial infarction associated with drug-eluting stents vs. bare-metal stents for individual trials and the pooled population. Hazard ratios are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log hazard ratio. DES, drug-eluting stent; BMS, bare-metal stent. (B) Kaplan–Meier curves of recurrent myocardial infarction in each of the stent groups for the pooled population.



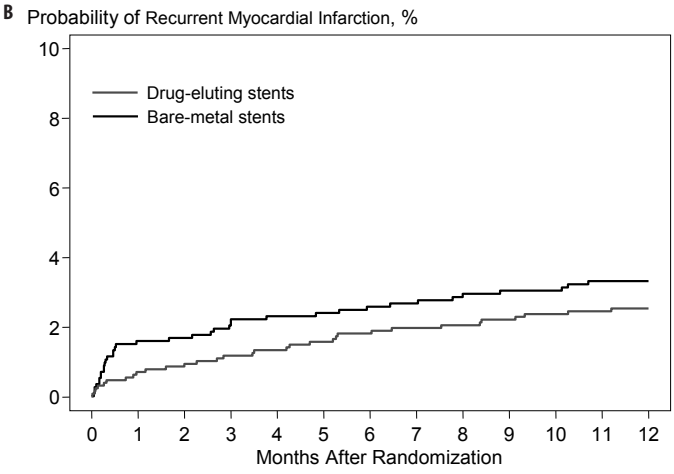


Figure 5A shows the absolute numbers of patients who suffered a recurrent myocardial infarction according to the treatment group, with the hazard ratio for each of these trials. No evidence of heterogeneity was observed across the trials (I^2=0%). Overall, use of the drug-eluting stent was associated with a hazard ratio for recurrent myocardial infarction of 0.72 (0.48 to 1.08), *P*=0.11, compared with use of the bare metal stent. Figure 5B shows one-year probability curves for recurrent myocardial infarction in the 2 treatment arms. The probability of recurrent myocardial infarction was 2.5% in the drug-eluting stent group and 3.3% in the bare-metal stent group.

The composite of death, recurrent myocardial infarction or reintervention was observed in 158 of the 1.474 patients in the drug-eluting stent group and 252 of the 1.312 patients in the bare-metal stent group. Use of the drug-eluting stent was associated with a hazard ratio for this composite end point of 0.53 (0.42 to 0.67), *P*<0.001, compared with use of the bare metal stent. The probability of the composite of death, recurrent myocardial infarction or reintervention was 9.5% in the drug-eluting stent group and 17.8% in the bare-metal stent group.

DISCUSSION

In this study, we performed a meta-analysis of 8 randomised trials comparing drug-eluting stents with bare metal stents in patients with acute ST-segment elevation myocardial infarction. We found no significant differences in the risk of stent thrombosis, death or recurrent myocardial infarction between patients treated with drug-eluting stents versus bare-metal stents. On the other hand, we found that treatment with drug-eluting stents was associated with a 62% reduction in the hazard of reintervention as compared with bare metal stents. The advantage of drug-eluting stents was notable within the first month after the stent implantation procedure and continued to increase thereafter.

A large number of studies have shown that the use of drug-eluting stents is associated with favourable outcomes in patients with various clinical and angiographic characteristics.[9,31] However, data on the outcome of patients undergoing primary PCI with implantation of drug-eluting stents have been limited and whether the favourable results obtained with drug-eluting stents in other settings also extend to patients with acute ST-segment elevation myocardial infarction has not been firmly established. A major concern with drug-eluting stents in this group of patients has been an increased risk for stent thrombosis, especially acute (within 24 hours of stent implantation) and subacute (within 30 days of stent implantation).[10] There is an increased platelet activation in acute coronary syndromes, especially in acute myocardial infarction,[32] and coronary stenting is associated with a more intense platelet activation than balloon angioplasty alone.[33] A greater platelet activation coupled to delayed healing, lack of endothelialisation, and exposure of proinflammatory and prothrombogenic environment of

the necrotic core could provide the rationale for an increased risk of drug-eluting stent thrombosis in patients with acute myocardial infarction.[10] Recently, Park et al.[12] found that primary stenting with implantation of sirolimus-eluting or paclitaxel-eluting stents in patients with acute myocardial infarction was a major predictor for acute and subacute stent thrombosis. However, registry studies of patients with acute ST-segment elevation myocardial infarction have not shown an increased risk of stent thrombosis with drug-eluting stents as compared with bare metal stents.[34-36]

In our meta-analysis, the incidence of stent thrombosis was similar among patients treated with drug-eluting stents versus bare-metal stents, as was the incidence of death or recurrent myocardial infarction. These findings support the safety of use of these stent types. However, they should be interpreted with caution. Despite the advantage conferred by meta-analysis which has the potential to increase the statistical power, the rare occurrence of the previously discussed adverse events might limit the capacity of this meta-analysis to detect a possible difference between the two treatment arms with regard to the safety outcomes. Larger studies with a longer follow-up period will be needed to definitely answer the question of whether primary stenting with drug-eluting stents is safe.[37,38]

CONCLUSION

In conclusion, the results of this meta-analysis show that the use of drug-eluting stents in patients undergoing PCI for acute ST-segment elevation myocardial infarction is safe and improves clinical outcomes by reducing the risk of reintervention compared with bare-metal stents.

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CHAPTER 8

THE EFFECT OF ITF-1697 ON REPERFUSION IN PATIENTS UNDERGOING PRIMARY ANGIOPLASTY. SAFETY AND EFFICACY OF A NOVEL TETRAPEPTIDE, ITF-1697.

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ABSTRACT

Aim ITF-1697 is a C-reactive protein-derived tetrapeptide that, based on pre-clinical studies, is thought to reduce reperfusion injury. We performed a dose-finding study to assess safety, preliminary efficacy and clinical outcome of prolonged i.v. infusion of ITF-1697 in patients with an acute myocardial infarction (AMI) who were eligible for percutaneous coronary intervention (PCI).

Methods and Results This was a multicenter dose-finding study that was randomised, double blind, and placebo-controlled. Four-hundred-and-two patients were enrolled. Intravenous infusion of four dosages of ITF-1697 (0.1, 0.5, 1.0 or 2.0 µg/kg/min) or placebo was started before PCI and continued for 24 hours. After interim analysis of data from 242 patients the study continued with the 0.1 and 1.0 µg/kg/min ITF-1697 regimes. Analysis did not raise any safety concerns. Post-procedure perfusion, assessed by TIMI flow, corrected TIMI frame count, blushgrade and ST-segment resolution, was similar for the placebo, 0.1 and 1.0 µg/kg/min regimes. Furthermore, the results showed no differences between the treatment regimes in enzymatic infarct size or clinical outcome up to 30 days.

Conclusion ITF-1697 was well tolerated. However, neither a dose-relation nor improvement of perfusion, clinical outcome or reduction of myocardial damage could be demonstrated with ITF-1697 during and after primary PCI for AMI.

INTRODUCTION

Acute myocardial ischaemia caused by thrombotic coronary occlusion leads to time-dependent loss of myocytes. Percutaneous coronary intervention (PCI) and thrombolytic therapy are effective and commonly used therapies to obtain early reperfusion in acute myocardial infarction (AMI).[1-3] Early reperfusion conveys tissue salvage, i.e. reduction in infarct size and preservation of left ventricular function, thereby improving short- and long-term outcome after AMI.[4] However, it is has been suggested that reperfusion itself can precipitate further myocardial injury, known as 'reperfusion injury'.[5-7] If this 'reperfusion injury' could be treated and eliminated, the outcome for patients with AMI might improve further.[8] Reperfusion injury is thought to be mainly mediated by an inflammatory response (polymorphonuclear neutrophil, complement and platelet activation), intracellular Ca^{+} overload and reactive oxygen species. Several pharmacological agents or adjunctive therapies have been used in the clinical setting to attempt to reduce the injury caused by these pathways.[9-13]

This report presents the first study investigating the effects of ITF-1697 on reperfusion injury in humans. ITF-1697 is a proprietary tetrapeptide Gly-(Et)Lys-Pro-Arg that corresponds to sequence 113-116 of C-Reactive Protein (CRP) and has been shown to exert anti-inflammatory actions and marked anti-anaphylactive properties.[14] ITF-1697 is a new substrate that showed

promising results in the pre-clinical phase to prevent reperfusion injury in AMI, mainly by inhibiting the inflammatory response. Experimental data, obtained in models of ischaemia and reperfusion, have shown that ITF-1697 prevents PMN adhesion and extravasation, preserves vascular endothelial phenotype and limits the increase in vascular permeability and loss of microcirculatory blood flow (unpublished data on file at Italfarmaco). For example, in the hamster cheek pouch model of microcirculation subjected to 30 min of ischaemia followed by reperfusion, ITF-1697 (1.0 µg/kg/min) virtually abolished microvascular damage (capillary leak, fluid extravasation, PMN adhesion and capillary plugging) and resulted in preservation of microcirculatory flow. Also, in a study in the in vivo dog heart, 0.83 µg/kg/min ITF-1697 (administered i.v. just prior to reperfusion after 90 minutes of coronary artery occlusion) reduced myeloperoxidase activity (reflecting reduced neutrophil activity) and decreased myocardial infarct size by 50% resulting in preservation of ejection fraction (unpublished data on file at Italfarmaco). Other *in vivo* studies in rat, rabbit, and dog showed improved survival with ITF-1697 with doses as low as 0.05 µg/kg/min, administered either before coronary artery ligation or just prior to reperfusion after coronary occlusion resulting in myocardial infarction.

Accordingly, it was hypothesized that ITF-1697 may provide benefit on top of optimal drug and interventional therapy in patients with acute ST elevation myocardial infarction. The present study was designed to assess safety, and to compare preliminary efficacy and clinical outcome of prolonged intravenous infusion of four doses of ITF-1697 and placebo during and after a primary PCI procedure in patients with acute myocardial infarction.

METHODS

The Protect Against Reperfusion Injury with ITF-1697 in acute Myocardial Infarction (PARI-MI) was a multicenter, randomised, double blind, placebo controlled, dose finding study conducted in eleven centres in Italy and The Netherlands between January and December 2001. The study was started comparing 4 doses ITF-1697 (0.1, 0.5, 1.0, 2.0 µg/kg/min) and placebo with about 50 patients in each group. After interim analysis the study was designed to continue with another 50 patients in each of 2 doses ITF-1697 and placebo. Thus, finally 3 groups of 100 patients each (2 doses ITF-1697 and placebo) and 2 groups of 50 patients each (ITF-1697) were to be enrolled.

Study population

Patients with typical symptoms of AMI and electrocardiographic (ECG) signs of a large or medium size infarction, who were eligible to undergo invasive revascularization through primary PCI, were included in the trial. Written informed consent was obtained from all patients and the study design was approved by the institutional ethics committees.

Patients of both sexes had to be at least 18 years of age and time from symptom onset to enrolment had to be within 12 hours. Chest pain had to last for at least twenty minutes and thrombolytic treatment prior to PCI was not allowed. In order to enrol patients with large and medium size AMIs ST segment elevation had to be ≥0.2 mV in two or more contiguous leads with the cumulative ST deviation ≥10 mV on a 12-lead ECG. Patients were excluded having a history of bleeding diathesis; major bleeding ≤30 days; major surgery ≤30 days; history of known hemorrhagic stroke at any time or any stroke ≤30 days; uncontrolled hypertension (>200/110 mmHg); participation in another trial; inability to perform 30 day follow up; pregnancy or women of childbearing potential; concomitant disease that interferes with prognosis; contra-indications to standard drugs for coronary intervention and coronary heart disease; weight >105 kg. Study medication was started in eligible patients after informed consent without further delay. When subsequent platelet count <60,000/mm^3 (<60x10^9 /L), hematocrit <30% or creatinine ≥2.9 mg/dL (≥177 µmol/L) indicated that the patient should have been excluded, the infusion of study medication was stopped. Nevertheless, the patient remained in the study and all measurements were performed according to the intention to treat principle.

Treatments

Patients were randomised by an Interactive Voice Response System to an 1-2 minutes i.v. loading dose followed by a continuous i.v. infusion of ITF-1697 in different doses (0.1, 0.5, 1.0, 2.0 µg/kg/min) or placebo. The intravenous loading dose was 11, 55, 110, and 220 µg/kg in the 0.1, 0.5, 1.0 and 2.0 µg/kg/min ITF-1697 treatment groups, respectively. The rationale for the dose regimen employed was based on (unpublished) animal data. In an in vivo dog heart study, ITF-1697 was injected intravenously starting with a slow bolus of 100 µg/kg (starting 10 min prior to reperfusion) followed by 0.83 µg/kg/min throughout the 4.5 h reperfusion protocol and markedly reduced myocardial infarct size (unpublished data on file at Italfarmaco). Study drug was started after enrolment prior to angiography, and continued up to 24 hours. PCI of the infarct related coronary artery was performed at the investigator's discretion. Aspirin was given daily starting on hospital admission with a loading dose of 300 to 500 mg. In the case of stenting, clopidogrel was given at a loading dose of 300 mg followed by 75 mg/day for four weeks. Concomitant treatment with (low molecular weight) heparin, glyco-protein IIb/IIIa inhibitors and all other therapies was at the investigator's discretion.

Safety

The safety endpoints were death, recurrent AMI, bleeding and other Serious Adverse Events (SAE) from hospital admission until 30 days. This was assessed by laboratory blood samples, routine ECG and an outpatient clinic visit at 30 days (23-37). All deaths were included (cardiac and non-cardiac) and classified whenever possible on the basis of an autopsy. Bleeding, including intracranial haemorrhage, was classified according to the TIMI criteria.[15] SAE's were

defined as any medical occurrence that resulted in death, life-threatening situations, hospitalisation or prolongation of the existing hospitalisation, or persisting significant disability.

Efficacy

The efficacy endpoints were myocardial perfusion and myocardial infarct size. Perfusion was assessed by TIMI flow grade,[16] corrected TIMI frame count (CTFC, corrected for 30 frames/second (f/s): LAD),[17] myocardial blush grade,[18] ST-segment resolution and recurrent ischaemia or recurrent AMI. With regard to the CTFC the distribution plot of TIMI frame counts were drawn for placebo and ITF 1697-treated patients. Values below 28 f/s were taken into account for defining normal reperfusion. Leftward shift of the mean frame count of at least 6 f/s was considered clinically significant. In case of an occluded vessel the maximum frame count measurement was scored. Two independent observers performed ST-segment analysis. The sum of ST segment elevation and depression was measured with lens-intensified callipers to the nearest 0.025 mV, 60 ms after the end of the QRS complex (J-point) of all 12 leads. Measurements were done at 1 and 3 hours after intervention.

Myocardial infarct size

Myocardial damage was estimated by the area under the curve of serial alpha-hydroxybutyrate dehydrogenase (HBDH).[19-21] Haemolysed samples were discarded. and all other measurements were performed centrally by independent, blinded, and qualified personnel in the core laboratory. The angiographic measurements, the ST-segment measurements, as well as infarct size analysis and calculation were all performed centrally by independent and qualified personnel in the core laboratory, blinded for treatment assignment.

Clinical outcome

Re-infarction was defined as a second rise in CK-MB or total CK ≥2 times the upper limit of normal and the onset of recurrent angina or new significant Q-waves of ≥0.04 seconds in duration or having a depth > one fourth of the corresponding R-wave amplitude in two or more contiguous leads.

Recurrent ischaemia was defined as 1) an episode of chest pain at rest, associated with new ST segment shift of ≥ 0.1 mV or T-wave inversion/pseudo-normalization in at least two contiguous leads, 2) chest pain resulting in an invasive cardiac intervention (including diagnostic catheterisation, intra-aortic balloon pump counterpulsation, PCI or Coronary Artery Bypass Graft (CABG)) within the same hospitalisation, or 3) readmission for unstable angina.

Statistical analysis

Two interim analyses were performed to evaluate safety and dose-response relationships in order to select two dosages for continuation and final analysis. With respect to preliminary efficacy assessment the following information regarding clinically significant changes in the

relevant parameters applied, based on the control group data versus the ITF-1697 treatment group: A TIMI flow grade 3 of 85 versus >90%[2], myocardial blush grade 3 of 25 versus >30%[18] and enzymatic infarct size of 4.4 versus <3.9 g-eq.[4] In addition, if any dose relationship in the incidence of adverse events seemed to be present, logistic regression analysis was used for trend analysis.

The first interim analysis was performed after 125 patients, and the second interim analysis after about 250 patients had received ITF-1697 infusion or placebo. The following criteria were applied: a) If dose-response was detected, two safe and effective dosages were to be selected. b) If a dose-response was not evident, the number of 50 patients per group allowed to have 90% statistical power to select the best dosage with respect to the aforementioned parameters of TIMI flow grade, blush grade and infarct size.[22] The final sample size of 100 patients for the 2 selected dosages and placebo allowed an estimate of two-sided 90% C.I. equal to ±10% for differences between the response rate of active doses and placebo.

Data were presented as mean ±SD, and for non-parametric measurements as median with percentiles. All analyses were performed comparing each active ITF-1697 dosage group separately with placebo. For discrete variables a Chi-square test was used. Binomial confidence intervals were constructed and a Fisher's Exact Test was performed to compare the incidence of adverse events of ITF-1697 with placebo. No adjustments were made for multiple testing. A Student's t-test was performed on normally distributed continuous data or a Wilcoxon rank test in case of skewed data distribution. Significance was defined as $P<0.05$.

Subgroup analyses.

Additional subgroups analysis was performed for gender; blush grade before procedure; ST-segment resolution; age (above or below median, < or ≥70 years); use of GPIIb/IIIa antagonist; time from onset of symptoms and intervention (≥ or <2 hours); infarct location; LAD or RCA as culprit lesion; infarct size (above or below median); and an event free history prior to the AMI.

RESULTS

Patient groups

A total of 402 patients were enrolled. Ten patients were excluded from the analysis: seven patients were randomised but did not receive study medication for various reasons, one other patient died shortly after randomisation before study medication was given, one patient refused written informed consent although he had given with oral consent in the presence of a witness, and one patient withdrew the informed consent before discharge. Finally 392 patients were enrolled and received study medication. After the first interim analysis the study was continued without modification. After the second interim analysis, with 242 patients, the

Table 1. Baseline Demographics

Characteristics	Placebo N = 92 (%)	0.1 ITF-1697 N = 93 (%)	1.0 ITF-1697 N = 94 (%)
Mean age — yr ± SD	61 ± 13	62 ± 11	60 ± 12
Male — (%)	76 (83)	70 (75)	79 (84)
Non smokers — (%)	29 (32)	33 (36)	29 (31)
Diabetes (N)IDD — (%)	11 (12)	9 (10)	17 (18)
Previous MI — (%)	17 (19)	11 (12)	14 (15)
Previous angina —(%)	20 (22)	15 (16)	14 (15)
Previous PCI —(%)	8 (9)	6 (6)	11 (12)
Previous CABG — (%)	2 (2)	1 (1)	2 (2)
Previous stroke — (%)			
Non-Hemorrhagic	1 (1)	3 (3)	3 (3)
TIA	2 (2)	4 (4)	3 (3)
Heart Failure (Killip Classification) — (%)			
Class I	82 (89)	92 (98)	84 (89)
Class II-IV	10 (11)	2 (2)	10 (11)

No significant differences between the groups.
(N)IDDM = (non) insulin dependent diabetes mellitus; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; TIA = transient ischaemic attack.

study was continued with the placebo, 0.1 and 1.0 µg/kg/min dose regimes. The 1.0 µg/kg/min ITF-1697 regime was chosen as it was closest to the 10% absolute difference in TIMI flow grade 3 indicated by the protocol. The 0.1 µg/kg/min ITF-1697 was chosen to maintain reasonable pharmacological interval. Ninety-two patients received placebo, 93 were treated with ITF-1697 0.1 µg/kg/min and 94 with 1.0 µg/kg/min. The treatment groups ITF-1697 0.5 and 2.0 µg/kg/min contained 55 and 58 patients, respectively. Baseline characteristics were similar between the groups (table 1). In total 18 patients did not undergo a PCI because of various reasons, and did not continue on study medication after the initial loading dose and infusion, hence were expelled from further analysis. Three of these patients underwent emergency coronary bypass surgery. Pre-procedurally there were no significant differences apparent, except for TIMI flow: the ITF-1697 1.0 treatment group contained a higher percentage of patients with an occluded vessel (TIMI flow grade 0, 1) at baseline. Because of this unbalanced distribution it was decided post-hoc to perform a subgroup analysis in 208 patients with occluded vessels treated with placebo, 0.1 or 1.0 µg/kg/min ITF-1697.

Angiographic results

A successful PCI procedure, indicated by a post-procedural epicardial TIMI flow grade 3, was achieved in the placebo, ITF-1697 0.1 and ITF-1697 1.0 group in 82%, 84% and 88%, respectively (table 2). Coronary stenting was performed in 84 (92%) of the placebo cases compared with 80 (85%) and 83 (89%) in the ITF-1697 0.1 and 1.0 group, respectively. GPIIb/IIIa antagonists were used in 122 patients, 44%. The median CTFC in the total population was 24 f/s. The results

Table 2. Angiographic and Angioplasty Results

Variable	Placebo	0.1 ITF-1697	1.0 ITF-1697
Total study population — no. (%)			
TIMI flow Pre-procedure	91	93	92
0-1	63 (69)	69 (74)	76 (83)*
2	13 (14)	14 (15)	13 (14)
3	15 (17)	10 (11)	3 (3)
p-value		*0.51*	*0.013**
TIMI flow Post-procedure	90	90	88
0-1	4 (4)	1 (1)	3 (3)
2	12 (13)	13 (14)	8 (9)
3	74 (82)	76 (84)	77 (88)
p-value		*0.63*	*0.34*
CTFC Pre-procedure	83	93	91
Median f/s (P25-P75)	173 (173-173)	173 (173-173)	173 (173-173)
p-value		*0.92*	*0.16*
CTFC Post-procedure	70	77	72
Median f/s (P25-P75)	24 (17-36)	26 (17-41)	24 (14-41)
p-value		*0.52*	*0.99*
Blushgrade Post-procedure	77	78	81
0-1	32 (41)	38 (49)	43 (53)
2	20 (26)	27 (35)	23 (28)
3	25 (33)	13 (17)	15 (19)
p-value		*0.16*	*0.13*
Subgroup TIMI flow grade 0, 1 pre-intervention — no. (%)			
TIMI flow Post-procedure	62	66	73
0-1	4 (6)	1 (2)	3 (4)
2	12 (19)	11 (17)	7 (10)
3	46 (74)	54 (82)	63 (86)
p-value		*0.25*	*0.09*
CTFC Post-procedure	49	57	58
Median f/s (P25-P75)	24 (19-46)	26 (17-43)	24 (14-42)
p-value		*0.97*	*0.62*
Blushgrade Post-procedure	53	56	81
0-1	20 (38)	29 (43)	36 (55)
2	14 (26)	18 (32)	18 (27)
3	19 (36)	9 (16)	12 (18)
p-value		*0.06*	*0.05*

p-value: ITF-1697 dosage compared with placebo.

*: statistically significant.

TIMI = thrombolysis in myocardial infarction; CTFC = corrected TIMI frame count.

of the angiographic measurements (TIMI flow, CTFC and blush grade) used as markers of reperfusion efficacy did not show any significant difference between the treatment groups.

Electrocardiographic results

ECG's at enrolment as well as at 1 vs. 3 hours post PCI were available in 372 patients (of the total of 392). There was no effect of either one of the ITF-1697 treatment regimes on the extent of ST-segment resolution (table 3).

Table 3. ECG resolution of ST-segment elevations at one and three hours after intervention

Variable	Placebo	0.1 ITF-1697	1.0 ITF-1697
Total study population — no. (%)			
1hr ST-resolution	72	69	83
Complete resolution	22 (31)	20 (29)	20 (24)
Partial resolution	22 (31)	30 (44)	36 (43)
No resolution	28 (39)	19 (28)	27 (33)
p-value		*0.45*	*0.96*
3hr ST-resolution	78	78	80
Complete resolution	29 (37)	30 (39)	23 (29)
Partial resolution	32 (41)	36 (46)	44 (55)
No resolution	17 (22)	12 (15)	13 (16)
p-value		*0.56*	*0.71*
Subgroup TIMI 0, 1 pre-intervention — no. (%)			
1hr ST-resolution	48	50	66
Complete resolution	11 (23)	15 (30)	15 (23)
Partial resolution	16 (33)	20 (40)	31 (47)
No resolution	21 (44)	15 (30)	20 (30)
p-value		*0.19*	*0.32*
3hr ST-resolution	53	56	64
Complete resolution	14 (26)	21 (38)	19 (30)
Partial resolution	27 (51)	27 (48)	35 (55)
No resolution	12 (23)	8 (14)	10 (16)
p-value		*0.15*	*0.43*

p-value: ITF-1697 dosage compared with placebo.

Complete resolution is ≥70% ST-segment resolution; Partial resolution is 30%-70% ST-segment resolution; No resolution is <30% ST-segment resolution; TIMI = thrombolysis in myocardial infarction.

Infarct size

The median enzymatic infarct size, as measured by the area under the HBDH curve in the total group was 5.2 g-eq. The infarct size for placebo, ITF-1697 0.1 and ITF-1697 1.0 and in the subgroup TIMI 0, 1 pre-intervention as shown in table 4 was not significantly different.

Table 4. Median enzymatic infarct size

Variable	Placebo	0.1 ITF-1697	1.0 ITF-1697
Total study population — no.	88	90	92
g-eq/L (P25-P75)	4.5 (3.2-9.1)	5.0 (3.2-7.3)	5.3 (3.6-9.8)
p-value		*0.84*	*0.36*
Subgroup TIMI 0,1 pre-intervention — no.	59	65	74
g-eq/L (P25-P75)	5.8 (3.7-9.1)	5.6 (3.7-9.4)	6.0 (3.9-11.2)
p-value		*0.98*	*0.24*

p-value: ITF-1697 dosage compared with placebo.

g-eq = gram equivalents; TIMI = thrombolysis in myocardial infarction.

Larger infarct size was found in the total population in the TIMI 0, 1 pre-intervention subgroup compared to TIMI 2, 3 pre-intervention.

Clinical outcome

Clinical endpoints did not raise any safety concerns in any group. Ten patients died during the initial hospitalisation. At thirty days there were 16 deaths reported (table 5). The occurrence of adverse events such as recurrent MI, CABG, or bleeding did not show significant differences between the regimes. After thirty days 10 (3.6%) patients had suffered from recurrent ischaemia. A combination of the endpoints of mortality, recurrent ischaemia or recurrent AMI did not reveal a treatment effect of ITF-1697 (table 5). Fifteen of the total of sixteen reported

Table 5. Endpoints: Events at 30 days

Variable	Placebo	0.1 ITF-1697	0.5 ITF-1697	1.0 ITF-1697	2.0 ITF-1697	ITF total
Total study population — no. (%)	92	93	55	94	58	300
Mortality	3 (3.3)	3 (3.2)	4 (7.3)	2 (2.1)	4 (6.9)	13 (4.3)
p-value		*1.0*	*0.43*	*0.68*	*0.43*	*0.77*
Recurrent MI	0	0	1 (1.8)	2 (2.1)	2 (3.4)	5 (1.7)
p-value		*1.0*	*0.37*	*0.50*	*0.15*	*0.60*
CABG	2 (2.2)	3 (3.2)	1 (1.8)	2 (2.1)	3 (5.2)	9 (3.0)
p-value		*1.0*	*1.0*	*1.0*	*0.38*	*1.0*
Bleeding	13 (14)	7 (7.5)	7 (13)	14 (15)	3 (5.2)	31 (10)
p-value		*0.16*	*1.0*	*1.0*	*0.11*	*0.35*
Mortality or MI or re-Ischemia	6 (6.5)	4 (4.3)	5 (9.1)	10 (11)	7 (12)	26 (8.7)
p-value		*0.54*	*0.75*	*0.43*	*0.25*	*0.66*
Subgroup TIMI 0, 1 pre-intervention — no. (%)	63	68	45	76	40	229
Mortality	3 (4.8)	2 (2.9)	4 (8.9)	2 (2.6)	4 (10)	12 (5.2)
p-value		*0.67*	*0.45*	*0.66*	*0.43*	*1.0*
Recurrent MI	0	0	1 (2.2)	2 (2.6)	2 (5.0)	5 (2.2)
p-value		*1.0*	*0.42*	*0.50*	*0.15*	*0.59*
Recurrent-Ischemia	1 (1.6)	1 (1.5)	0	5 (6.6)	2 (5.0)	8 (3.5)
p-value		*1.0*	*1.0*	*0.22*	*0.56*	*0.69*

p-value: ITF-1697 dosage compared with placebo.

MI = myocardial infarction; CABG = coronary artery bypass grafting TIMI = thrombolysis in myocardial infarction.

deaths had TIMI flow grade 0, 1 pre-intervention. Recurrent myocardial infarction or recurrent ischaemia was not evidently higher in this subpopulation compared with those having TIMI 2, 3 flow pre-intervention.

Subgroup analysis

Analysis of the before mentioned subgroups on safety and efficacy between either one of the treatment groups compared with placebo did not reveal a dose response relation. Also, the angiographic outcome in the TIMI flow grade 0, 1 pre-intervention subgroup showed no significant differences, albeit a trend was observed for post-procedural TIMI flow in favour of both ITF-1697 treatment groups. The CTFC and blush grade did not differ significantly in this subgroup. In fact, the latter showed a possible adverse trend (table 2).

DISCUSSION

The principal finding of the present study was that prolonged i.v. administration of ITF-1697 as an adjunct to primary angioplasty was well tolerated and without safety concerns. In fact, the mortality after a large AMI in the total study population was low (4.1% at 1 month), which compares favourably with the overall 8.4% one-month mortality after myocardial infarction in the European Heart Survey.[23] Overall ITF-1697 did not appear to exert a significant effect on indices of reperfusion (TIMI flow grade, CTFC, or blush grade), ST-segment resolution, myocardial infarct size, or clinical outcome, and no dose response was apparent. However, a trend towards better TIMI flow post-procedure was observed in the ITF-1697 1.0 µg/kg/min dose group. Furthermore, there appeared to be an imbalance in the number of patients with occluded infarct related vessels at angiography (TIMI flow 0, 1). These patients showed a larger infarct size and a higher mortality rate. In a separate analysis of patients with an initially occluded vessel a possible dose-effect relation was observed for post-procedural TIMI flow in favour of both ITF-1697 treatment groups. However, no such trends were apparent for reperfusion, infarct size or clinical outcome, while blush grade even showed a possible adverse trend (table 2). Future studies might investigate whether the latter observations in patients with an initially occluded vessel are true, or a chance finding.

Reperfusion injury: Purported mechanisms

Reperfusion is the only intervention that has been proven to halt the process of myocardial infarction after coronary artery occlusion. However, benefits of reperfusion may be limited by untoward effects, termed "reperfusion injury".[5-8] The mechanism of reperfusion injury is not completely understood, but may include (*i*) cytosolic and mitochondrial Ca^{+}-overload, (*ii*) massive release of reactive oxygen species, (*iii*) damage to the extracellular matrix, (*iv*) impaired cellular energetics, and (*v*) an acute inflammatory response.[5,8,24,25] The latter involves

recruitment of polymorphonuclear neutrophils (PMN), complement and platelet activation, and disturbed endothelial function, which leads to increased permeability and results in more necrosis and myocardial damage. Recruitment and activation of PMN results in capillary plugging (thereby mechanically blocking flow), capillary leakage and enhancement of generation of reactive oxygen species, together culminating in secondary impairment of microcirculatory flow ("no-reflow" phenomenon) despite initial restoration of epicardial coronary patency and blood flow.[24-27] The occurrence of no-reflow correlates with increased final infarct size and a poorer long-term clinical outcome.[28,29] Consequently, targeting one or more of the above mentioned mechanisms could further improve the benefit of early reperfusion.

Apparent lack of effect of ITF-1697 in patients with myocardial infarction

Results from different animal models of reperfusion injury indicated that with ITF-1697 the infarct size, occurrence of ventricular tachycardias and fibrillation as well as mortality was reduced. These beneficial effects were observed in models in which the substrate was administered before and during ischaemia as well as when administered at the time of reperfusion (unpublished data on file at Italfarmaco). In contrast to these findings the present study showed neither consistent benefit nor a dose-effect relation of ITF-1697 on indices of perfusion after direct PCI. To detect a dose-response in this study population an extensive prospectively prescribed statistical analysis was developed, unfortunately this analysis could not demonstrate a dose-response. Several factors may contribute to the discrepancy between animal experiments and the present study in humans.

Collateral blood flow

Collateral blood flow is an important determinant of infarct size.[30] In the AMISTAD trial the authors speculated that the benefit of adenosine (as an adjunct to thrombolysis) which occurred selectively in patients with an anterior AMI, could be attributed to collateral flow.[10] In contrast, the present study failed to reveal any evidence of a differential outcome in patients with culprit lesions in either RCA or LAD.

Timing of administration

It could be argued that ITF-1697, administered prior to, during and after PCI, did not reach the jeopardized myocardium in sufficient concentrations prior to the onset of reperfusion, except perhaps via microvascular collateral vessels that are undetectable by coronary angiography.[31,32] Yet, it should be appreciated that ITF-1697 was infused intravenously several minutes before PCI was performed. This should give ample time to achieve adequate plasma levels of ITF-1697, so that at the time of onset of reperfusion most neutrophils should have been exposed to ITF-1697. The apparent lack of benefit in patients with an open IRV at angiography may be related to the timing of drug administration, since in those patients spontaneous reperfusion

had already occurred, implying that ITF-1697 was administered at a considerable time after (partial) reperfusion.

Duration of ischaemia

In a previous study in dogs, ITF-1697 limited myocardial infarct size when administered just prior to reperfusion after up to 90 minutes coronary artery occlusion. In contrast, in the present study coronary artery occlusions lasted more than two hours. It is possible that ischaemia-related damage predominates in patients with such prolonged coronary occlusion (which is typical for clinical studies), with few cardiomyocytes left to be affected by reperfusion injury.[31] Consequently, little effect might then be expected of reperfusion injury limiting strategies. This may, at least in part, explain why over the past few years several pharmacological agents that have shown considerable promise in the experimental setting have failed to show any benefit in the clinical setting of ischaemia and reperfusion.[9,11-13] However, even when we analysed the subgroup of patients that had re-established flow within two hours of symptom onset, no benefit was observed.

Presence of pre-infarct angina

Another important difference between the clinical and experimental setting is that the myocytes used in animal studies are, in contrast to human coronary arteries, generally not subjected to the process atherosclerosis, endothelial dysfunction and/or myocardial ischaemia prior to the sustained coronary artery occlusion.[27,31] It is thus possible that patients, particularly those that experience angina prior to infarction, are protected via 'ischemic-preconditioning',[33,34] so that less additional benefit of ITF-1697 might be expected. However, also in patients with an event free history prior to the AMI no benefit of ITF-1697 was observed in the present study.

Micro-embolization

Another consequence of the process of atherosclerosis in the human heart versus coronary artery ligation in experimental animals,[26,31] is that impaired post-procedural perfusion or the no-reflow phenomenon could be, at least in part, the result of embolization of plaque debris into the distal microvasculature rather than of reperfusion injury.[35-38]

Co-medication

It may be hypothesized that treatment with heparin and GPIIb/IIIa blockers may influence the effect of ITF-1697 on adherence and extravasation of PMNs and possibly on endothelial permeability.[39-41] Subgroup analysis did not support such a hypothesis, as we did not observe any effect of ITF-1697 in patients who did or did not receive heparin and GPIIb/IIIa blockers.

Doses of ITF-1697

The highest dose used in the current trial (2.0 μg/kg/min) was 2.4 fold higher then the dose the limited infarct up to size 50% in the dog. Nevertheless, it is possible that the dose regimes that were employed in this study may not have been optimal in humans.

Sample size

The sample size used was large enough for safety assessment and dose effect detection, but not large enough to conclude definitely whether ITF-1697 administration, as an adjunct to primary PCI, can modulate reperfusion. We do realise that an effect of ITF-1697 could have been missed in this relatively small study. Furthermore, it should be appreciated that this study was rather complex, concerning many different measurements in patients admitted with myocardial infarction. Because of this complexity measurements were incomplete in part of the patients. Yet, the primary angiographic endpoints were complete in 84% (blushgrade) to 96% (TIMI flow grade) of the patients.

CONCLUSION

Reperfusion injury in clinical practice

The concept of reperfusion injury has been clearly demonstrated in many experimental studies, although even in those studies data are not fully consistent.[8,24,25,31,42] In contrast, in clinical myocardial infarction, the importance of reperfusion injury has not been established. In fact, clinical studies with anti-inflammatory drugs,[11,13] Na^+/H^+ exchange inhibitors,[9] glucose-insulin-potassium,[12,43,44] and adenosine[10,45] so far led to inconclusive results. This in mind, one might raise the question that possibly treatment in clinical practice is too late to reduce reperfusion injury or that there is no (relevant) reperfusion injury in humans, and thus no clinical benefit of decreasing such injury. Similarly, the PARI-MI study did not reveal a clear benefit, and no dose-relation, even though higher dosages were studied than in the pre-clinical studies, in which ITF-1697 was shown to be beneficial. The main reason for discrepancy between animal and human findings would be the different pathophysiologic context in which the drug was tested, leaving open the hypothesis that the drug might have beneficial effects in different pathophysiological settings, more appropriate for the drug activity.

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CHAPTER 9

RESULTS OF THE FIRST CLINICAL STUDY OF ADJUNCTIVE CALDARET (MCC-135) IN PATIENTS UNDERGOING PRIMARY PERCUTANEOUS CORONARY INTERVENTION FOR ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION: THE RANDOMISED MULTICENTER CASTEMI STUDY

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ABSTRACT

Aims To examine the safety and efficacy of intravenous caldaret in patients with large acute ST-elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI).

Methods and results STEMI patients (n=387) with ≥10 mm summed ST-deviation on electrocardiogram were randomized to receive a 48 h infusion of caldaret 57.5 mg [lower dose (LD)], caldaret 172.5 mg [higher dose (HD)], or placebo, starting before PCI. Both HD and LD were well tolerated. In 247 patients with pre-PCI TIMI 0/1, there was no effect of HD or LD on single photon emission computed tomography infarct size or ejection fraction assessed at Day 7 and Day 30. Subgroup analyses suggest that future work in patients with anterior MI might be warranted.

Conclusion This first human experience with caldaret prior to direct PCI for large STEMI shows a good safety profile. No evidence of efficacy was discerned. Subgroup analyses in anterior MI patients showed some effects in endpoints studied, however, these findings require confirmation in a further study if a drug effect is to be established.

INTRODUCTION

Percutaneous coronary intervention (PCI) for patients with acute ST-elevation myocardial infarction (STEMI) achieves high epicardial recanalization rates and low mortality.[1,2] Even when epicardial reperfusion is successful, microvascular 'reperfusion injury' may account for up to 50% of the final infarct size and mechanisms of reperfusion injury may include intracellular calcium overload.[3-5] Acidotic conditions associated with ischaemia and reperfusion activate the Na^+/H^+ exchanger, and Na^+ extrusion is prevented by inhibition of Na^+/K^+ ATP-ase, leading to elevated intracellular sodium levels, which in turn increase intracellular calcium levels via Na^+/Ca^{2+} exchange.[3,6] Calcium overload contributes to cell death, myocardial hypercontracture, and arrhythmias.[7] Damage by reperfusion injury may also be mediated by other cell-mediated processes.[3,4,8]

Therapies targeting reperfusion injury might reduce infarct size and improve outcomes.[4,9-11] In animal models, caldaret (5-methyl-2-[piperazine-1-yl] benzenesulfonic acid monohydrate; MCC-135) inhibits intracellular calcium overload induced by ischaemia and reperfusion,[12] enhances calcium uptake into and inhibits calcium leakage from the sarcoplasmic reticulum,[13,14] and is selective for ischaemic myocardium.[13] In reperfusion models, caldaret reduces myocardial infarct size,[15] decreases cardiac markers,[16] and improves left ventricular (LV) function.[16] To test the theoretical benefit of caldaret, as an indirect calcium scavenger and an adjunct to direct PCI for STEMI, a pilot study of the safety and effectiveness of two doses of caldaret compared with placebo was conducted in human subjects.

METHODS

Dose

In this study, 57.5 mg caldaret [lower dose (LD) group], 172.5 mg caldaret [higher dose (HD) group], or placebo as a 45 min loading infusion (40 mL/hour) started prior to PCI, followed by maintenance infusion (4.2 mL/hour) for 24-48 h (minimum requirement of 24 h), was utilized in this study. These doses covered the anticipated therapeutic dose range, based on cardiovascular pharmacology studies in dogs, and a previous Phase I trial in healthy volunteers, which demonstrated that intravenous caldaret at doses up to the HD used were safe and well tolerated.

Trial design

CASTEMI, a multicentre, randomized, double-blind, placebo-controlled trial, examined the safety and efficacy of intravenous infusions of caldaret in patients undergoing primary PCI for STEMI. Caldaret was administered in addition to accepted standard therapy.

Within 6 h of the onset of symptoms of STEMI, eligible patients were randomized unstratified in blocks of six (1:1:1) using an interactive voice recognition system to receive LD, HD, or placebo. Coronary angiography determined thrombolysis in myocardial infarction (TIMI) flow grade prior to PCI. Angiograms were assessed by a blinded angiographic core laboratory (Heart Core, Leiden, The Netherlands). Efficacy endpoints and clinical evaluations were performed on Days 1-5, Day 7 [or discharge, if sooner (Day 7/discharge)], and Day 30. The PCI technique used followed local protocol.

Patient population

Patients were enrolled between April 2002 and February 2003 in 29 centres in Belgium, Germany, Israel, The Netherlands, and Spain. The study complied with the Declaration of Helsinki, was approved by local Ethics Committees, and written informed consent obtained from all patients.

Inclusion criteria

Inclusion criteria: male or female patients ≥18 years of age (≥35 years in Germany) with ongoing chest pain of ≥20 min, presenting within 6 h of onset of symptoms; confirmatory electrocardiogram (ECG) showing a large STEMI defined as ST-segment elevation of ≥0.2 mV (2 mm) in two contiguous anterior or extremity leads, and ≥1.0 mV (10 mm) summed from all leads; with a vascular access suitable for angiography.

Exclusion criteria

Major exclusion criteria: fibrinolytic therapy for the index infarct; previous MI overlapping the location of the index MI; cardiogenic shock unresponsive to intravenous fluid; severe conges-

tive heart failure (CHF; NYHA grade IV); known renal dysfunction (serum creatinine >1.5 x upper limit of normal); cerebrovascular event within the past 6 months; current therapy with catecholamines, phosphodiesterase inhibitors, or calcium sensitizers.

Study endpoints

Safety assessments

The safety population comprised 381 (98.4%) of 387 patients receiving study infusions. Safety endpoints were frequency and nature of treatment-related treatment-emergent adverse events (TEAEs); 30-day mortality; vital signs and laboratory safety; heart rhythm, conduction abnormalities, and ST-segment recovery by continuous 12-lead digital ECG monitoring over 24 h from the onset of drug infusion (eECG Core Laboratory, Duke University Medical Center, Duke Clinical Research Institute, NC, USA). An independent Data and Safety Monitoring Committee reviewed safety data during the study. Safety analyses were performed in all patients treated regardless of initial TIMI flow.

Efficacy measures

Efficacy analyses, prospectively defined, included 247 patients with initial TIMI 0/1 flow. The primary efficacy endpoint was infarct size, determined by single photon emission computed tomography (SPECT) on Day 7/discharge in patients with pre-PCI TIMI flow grade 0/1. Resting SPECT imaging was obtained using 22-25 mCi ^{99m}Tc-sestamibi and analysed in a blinded core laboratory (Heart Core, Leiden, The Netherlands) using Quantitative Gated SPECT and Quantitative Perfusion SPECT analytical packages (Software version 1.0, Cedars-Sinai Medical Center, Los Angeles, CA, USA) on a UNIX system. All participating centres were tested by the core laboratory to verify the quality of SPECT images.

Secondary endpoints:

- Area under the concentration–time curve (AUC) for total creatine kinase (CK) and its MB isoenzyme (CK-MB) to 72 h; for troponin T (TnT) and lactate dehydrogenase (LDH) to Day 5 (Quest Diagnostics, Heston, UK or St George's Hospital, London, UK).
- Infarct size on Day 30; LV end-systolic volume (LVESV) and LV enddiastolic volume (LVEDV) on Day 7/discharge and Day 30; global LV ejection fraction (LVEF) on Day 7/discharge and Day 30, determined by SPECT.
- Clinical endpoints, adjudicated by an independent blinded committee (Dr Marc A. Pfeffer, Brigham and Women's Hospital Cardiovascular Division, Boston, MA, USA), consisted: all-cause mortality, cardiac mortality, and resuscitated sudden death up to Day 30; CHF and re-admission for CHF up to Day 30; stroke and re-infarction up to Day 30; composite clinical endpoint up to Day 30, consisting of time to event for major adverse cardiovascu-

lar events (death, re-infarction, revascularization procedures, CHF, and re-admission for CHF).

- Blood samples at intervals up to 72 h measured caldaret concentrations (Covance Laboratories Ltd, Harrogate, UK).

Sample size and statistical analyses

The safety set analyses includes all randomized patients who received at least one dose or partial dose of study medication; the full analysis population included all randomized patients who received any study medication and who provided any efficacy data after the start of study medication. Following the principle of intention-to-treat, the full analysis TIMI 0/1 population were patients who were defined as the full analysis population who also recorded a TIMI 0/1 flow at entry.

Assuming SPECT infarct size standard deviation of 20%, and 20% of patients being unevaluable at Day 7/discharge, 240 patients with pre-PCI TIMI flow grade 0/1 provide a 80% power to detect a mean absolute difference of 10% in infarct size between caldaret and placebo. An estimated 60% of patients would have pre-PCI TIMI flow grade 0/1, giving a final sample size of ~ 400.

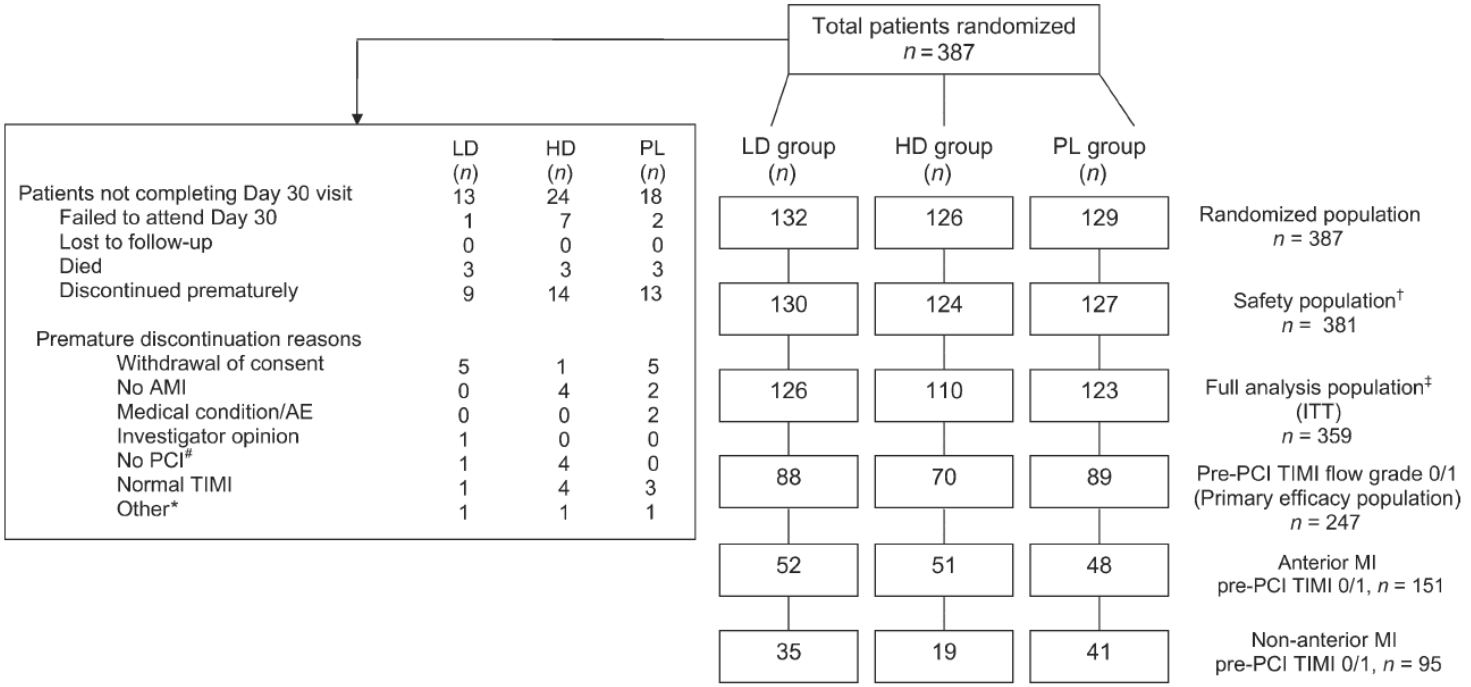
Analyses included pairwise comparisons between each active treatment group and placebo. Statistical tests were two-sided, at the 5% level of significance, and differences between treatment groups were presented with 95% confidence intervals. No adjustment was made for multiple comparisons, since this was an exploratory study - the emphasis was on estimation of differences vs. placebo.

Primary and secondary efficacy variables were log-transformed and analysed using analysis of covariance, including factors for centre, age, and treatment. Statistical analyses were performed with the SAS software Version 8.2. Further exploratory analysis was performed to identify other significant covariates (advanced age >70, gender, hypertension, diabetes mellitus, prior MI, angina, summed ST, location of infarct anterior/non-anterior) pre-specified in the analysis plan. No estimation of missing values was conducted. Efficacy data were missing due to deaths, withdrawals and non-evaluable SPECT, and numbers in each treatment group were similar; however, potential bias cannot be completely ruled out.

RESULTS

Patient population

Figure 1 describes patient disposition. Of note was the lower number of patients with non-anterior MI in the HD group. Baseline characteristics were well balanced (Table 1). A higher incidence of pre-PCI TIMI flow grade of 0 in the placebo group was detected (Table 2).



	LD (*n*)	HD (*n*)	PL (*n*)
Patients not completing Day 30 visit	13	24	18
Failed to attend Day 30	1	7	2
Lost to follow-up	0	0	0
Died	3	3	3
Discontinued prematurely	9	14	13
Premature discontinuation reasons			
Withdrawal of consent	5	1	5
No AMI	0	4	2
Medical condition/AE	0	0	2
Investigator opinion	1	0	0
No PCI[#]	1	4	0
Normal TIMI	1	4	3
Other*	1	1	1

Figure 1. Patient disposition (infarct location unknown in one patient).

[†]**n=6 did** not receive study treatment; [‡]n=16, PCI not performed; n=6, data not available.

[#]**CABG, thrombolysis,** lesion large/impenetrable.

[*]**Includes non-compliance** with exclusion criteria (previous MI in the same location as the index MI), PCI completed before infusion start, problems with IVRS.

Table 1. Patient characteristics

Baseline characteristics	Safety population	Pre-PCI TIMI flow grade 0/1 efficacy population (n = 247)		
	n = 381	LD, n = 88[a]	HD, n = 70	Placebo, n = 89
Age, years [mean (SD)]	60 (13)	60.0 (11)	61 (13)	59 (13)
Male — (%)	303 (80)	71 (81)	53 (76)	76 (85)
Weight, kg [mean (SD)]	78 (13)	82 (15)	78 (13)	80 (14)
Body mass index, kg/m2 [mean (SD)]	27 (3.7)	28 (4.2)	26 (3.4)	27 (3.3)
Hypertension — (%)	151 (40)	33 (38)	25 (36)	37 (42)
Diabetes — (%)	69 (18)	16 (18)	14 (20)	14 (16)
Hypercholesterolaemia — (%)	157 (41)	31 (35)	25 (36)	41 (46)
Current cigarette smoking — (%)	194 (51)	40 (46)	36 (51)	45 (51)
Prior PCI — (%)	28 (7.3)	6 (6.8)	6 (8.6)	8 (9.0)
Congestive heart failure — (%)	6 (1.6)	2 (2.3)	1 (1.4)	0
Prior MI — (%)	29 (7.6)	5 (5.7)	7 (10)	9 (7.9)
Anterior MI — (%)	239 (63)	53 (60)	51 (73)	48 (54)
Summed ST-elevation at screening, mm [median (range)]	n/a	17 (4.0–67)	18 (5.5–47)	19 (3.0–46)
Time to treatment				
Pain to hospital, min [median (range)]	n/a	113 (18–360)	118 (30–318)	114 (12–348)
Pain to start of study drug, min [median (range)]	n/a	163 (60–558)	169 (48–372)	166 (78–378)
Pain to first balloon, min [median (range)]	n/a	206 (84–390)	211 (78–438)	199 (102–426)
Hospital to first balloon, min [median (range)]	n/a	85 (18–234)	90 (18–198)	85 (36–174)
Start of study drug to first balloon, min [median (range)][b]	n/a	35 (-17–81)	35 (-6–143)	34 (-2–100)

MI, myocardial infarction; n/a, not available; SD, standard deviation.

[a]Infarct location unknown in one patient; [b]Negative number indicates balloon achieved prior to study drug administration.

Table 2. Pre-procedure TIMI flow grades, full analysis population

Variable	LD n = 126 (%)	HD n = 110 (%)	Placebo n = 123 (%)
TIMI flow grade			
0	69 (55)	56[a] (51)	80[a] (65)
1	19 (15)	14 (13)	9 (7.4)
0/1	88 (70)	70 (64)	89 (72)
2	23 (18)	30 (28)	20 (17)
3	14 (11)	10 (9.2)	13 (11)
2/3	37 (30)	40 (37)	33 (27)
Missing	1 (<1)	0	1 (<1)

[a]Data from one patient from local rather than core laboratory assessment.

Safety assessments

Mortality at Day 30 was 2.4%, with no difference between treatment groups (Table 3). The most frequently reported treatment-related TEAEs (possible or probable relationship to study

Table 3. Overview of AEs (safety population)

Events	LD	HD	Placebo	Total
	N = 130 (%)	N = 124 (%)	N = 127 (%)	N = 381 (%)
Deaths	3 (2.3)	3 (2.4)	3 (2.4)	9 (2.4)
All TEAEs	116 (89)	115 (93)	118 (93)	349 (92)
Severe TEAEs	24 (19)	20 (16)	30 (24)	74 (19)
Treatment-related TEAEs[a]	15 (12)	13 (11)	22 (17)	50 (13)
Most frequently reported severe intensity[b] TEAEs				
Cardiogenic shock	6 (4.6)	2 (1.6)	5 (3.9)	
Ventricular fibrillation	0	4 (3.2)	6 (4.7)	
Cardiac failure congestive	4 (3.1)	0	3 (2.4)	
Cardiac failure unspecified	2 (1.5)	2 (1.6)	2 (1.6)	
Hypotension	3 (2.3)	2 (1.6)	1 (0.8)	

[a]Possibly or probably related to study drug.

[b]Missing intensity assessments were set to severe for six patients (two in each treatment group).

drug) were hypotension, bradycardia, angina pectoris, headache and, vomiting; however, frequency of each was the same for drug and placebo groups.

Three patients withdrew from the study due to adverse events (AEs)/medical conditions and 8% of patients had interruption or discontinuation of the study drug due to a TEAE. Only one AE was considered by the investigator to be 'probably' related to study drug, an SAE of cardiac failure in the placebo group.

Table 4. Myocardial infarct size at Day 7/discharge and at Day 30 in patients with pre-PCI TIMI flow grade 0/1 determined by SPECT

Population	Day 7/discharge			Day 30		
	LD, n = 88	HD, n = 70	Placebo, n = 89	LD, n = 88	HD, n = 70	Placebo, n = 89
n[a]	71	54	73	71	56	68
Arithmetic mean (SD), %	19.5 (14.5)	22.1 (14.3)	20.0 (14.6)	16.8 (13.1)	19.5 (13.1)	16.1 (13.1)
LS mean (SE), %	19.5 (1.7)	23.5 (1.9)	21.6 (1.7)	17.1 (1.5)	20.6 (1.7)	17.7 (1.6)
Ratio of LS mean[b] (95% CI)	0.90 (0.7-1.1)	1.09 (0.9-1.3)	—	0.97 (0.7-1.2)	1.17 (0.9-1.4)	—
P-value	*0.348*	*0.438*	—	*0.783*	*0.194*	—
Reasons for missing SPECT infarct size data (TIMI 0/1)[a]						
Medical condition	8	2	4	4	1	6
SPECT imaging problems	6	10	5	9	11	8
Withdrawal of consent	1	1	5	3	1	6
Death	1	1	0	1	1	1
Other[c]	1	2	2	0	0	0
Total	17	16	16	17	14	21

CI, confidence interval; LS, least square; SE, standard error.

[a]The number of patients in which a SPECT was performed; [b]Calculated as LD/PL; [c]SPECT not available.

Table 5. Cardiac markers of infarct size in patients with pre-PCI TIMI flow grade 0/1

Variable	LD n = 88	HD n = 70	Placebo n = 89
CK, n[a]	83	68	86
Mean[b] (SD) AUC_{0-3d}, IU/L	965 (726)	977 (1143)	1146 (910)
Ratio (95% CI)	0.82 (0.67-1.02)	0.84 (0.68-1.05)	—
P-value	*0.071*	*0.136*	—
CK-MB, n[a]	84	68	86
Mean[b] (SD) AUC_{0-3d}, IU/L	44 (26)	44 (31)	48 (30)
Ratio (95% CI)	0.90 (0.74-1.08)	0.90 (0.73-1.10)	—
P-value	*0.26*	*0.292*	—
TNT, n[a]	84	68	87
Mean[b] (SD) AUC_{0-5d}, *mg*/L	4.2 (3.4)	4.1 (3.3)	4.3 (3.4)
Ratio (95% CI)	0.94 (0.78-1.15)	0.90 (0.73-1.12)	—
P-value	*0.566*	*0.347*	—
LDH, n[a]	83	68	87
Mean[b] (SD) AUC_{0-5d}, IU/L	493 (274)	497 (257)	514 (260)
Ratio (95% CI)	0.94 (0.82-1.09)	0.95 (0.82-1.10)	—
P-value	*0.423*	*0.492*	—

[a]Number of patients with data available for analysis; [b]Weighted geometric mean.

Table 6. LV function parameters determined by SPECT on Day 7/discharge and on Day 30 in patients with pre-PCI TIMI flow grade 0/1

Variable	Day 7/discharge			Day 30		
	LD, n = 88	HD, n = 70	Placebo, n = 89	LD, n = 88	HD, n = 70	Placebo, n = 89
n[a]	64	52	70	64	52	70
LVESV						
Mean[b] (SD), mL	77 (33)	81 (40)	91 (52)	77 (40)	82 (41)	86 (46)
Ratio (95% CI)	0.93 (0.78-1.10)	0.95 (0.79-1.13)	—	0.91 (0.76-1.09)	0.99 (0.82-1.19)	—
P-value	*0.377*	*0.550*	—	*0.307*	*0.920*	—
LVEDV						
Mean[b] (SD), mL	125 (38)	131 (46)	141 (57)	130 (43)	135 (48)	140 (53)
Ratio (95% CI)	0.91 (0.80-1.02)	0.93 (0.82-1.05)	—	0.94 (0.82-1.06)	0.97 (0.85-1.10)	—
P-value	*0.106*	*0.278*	—	*0.313*	*0.662*	—
LVEF						
Mean[b] (SD), mL	40 (11)	41 (12)	39 (12)	43 (13)	42 (11)	42 (12)
Ratio (95% CI)	1.02 (0.92, 1.12)	1.03 (0.92, 1.14)	—	1.05 (0.95, 1.15)	1.00 (0.90, 1.10)	—
P-value	*0.683*	*0.567*	—	*0.331*	*0.964*	—

[a]Number of patients with data available for analysis; [b]Arithmetic mean.

The median time to stable ST-segment resolution of 1.6, 1.3, and 1.4 h were not significantly different for the LD, HD, and placebo groups, respectively. No differences in QT_c or cardiac rhythm were observed.

Efficacy analyses

Infarct size, LV function, clinical endpoints

In patients with initial TIMI 0/1 flow, there was no difference between caldaret treatment and placebo Day 7/discharge and Day 30 infarct size by SPECT (Table 4). SPECT assessment occurred between Days 5 and 9 in the majority (87.8%) of patients, 11 patients having SPECT on Day 10 or later and 17 patients on Day 4 or earlier. There were also no differences in secondary endpoints of MI size by serum marker AUCs of CK, CK-MB, TnT, and LDH (Table 5); LVEF, LVESV, or LVEDV at either Day 7/discharge or Day 30 (Table 6); 30-day mortality, major adverse cardiovascular events, or new/worsening CHF (Table 7); heart rate, systolic and diastolic pressure at Day 7/discharge.

Table 7. Clinically adjudicated endpoints up to Day 30 in patients with pre-PCI TIMI flow grade 0/1

Events	LD n = 88 (%)	HD n = 70 (%)	Placebo n = 89 (%)
Endpoint			
Cardiac mortality	1 (1.1)	1 (1.4)	1 (1.1)
Non-cardiac mortality	0	0	0
Resuscitated sudden death	1 (1.1)	1 (1.4)	1 (1.1)
CHF	19 (22)	14 (20.0)	14 (16)
Re-admission for CHF	3 (3.4)	1 (1.4)	2 (2.2)
Re-infarction	4 (4.5)	1 (1.4)	1 (1.1)
Stroke	1 (1.1)	0	0
Composite clinical endpointa	28 (32)	15 (21)	20 (23)

[a]Consisted of major adverse cardiovascular events (death, re-infarction, revascularization procedures, CHF, and re-admission for CHF).

Subgroup analyses

Prospectively planned stepwise regression analyses of the efficacy endpoints identified that infarct location had a highly significant (P <0.0001) effect on the primary efficacy parameter compared with other covariates. Figures 2 and 3, respectively, describe the treatment effects in the subgroup of anterior and non-anterior MI patients with initial TIMI 0/1 flow. The composite clinical endpoint (MACE, CHF, and re-admission for CHF) was 22 (42.3%), 14 (27.5%), and 13 (27.1%) patients in the anterior MI-LD, HD, PL groups, respectively, up to Day 30. Higher cardiac marker values in the TIMI 0/1 placebo group were not due to the higher proportion of placebo TIMI 0 patients as analyses for patients with TIMI 0 showed both CK and CK-MB geometric mean values were still lower with drug than with placebo (CK: HD 11.5%; LD 16.2%, and CKMB: HD 10.6%; LD 9.9%).

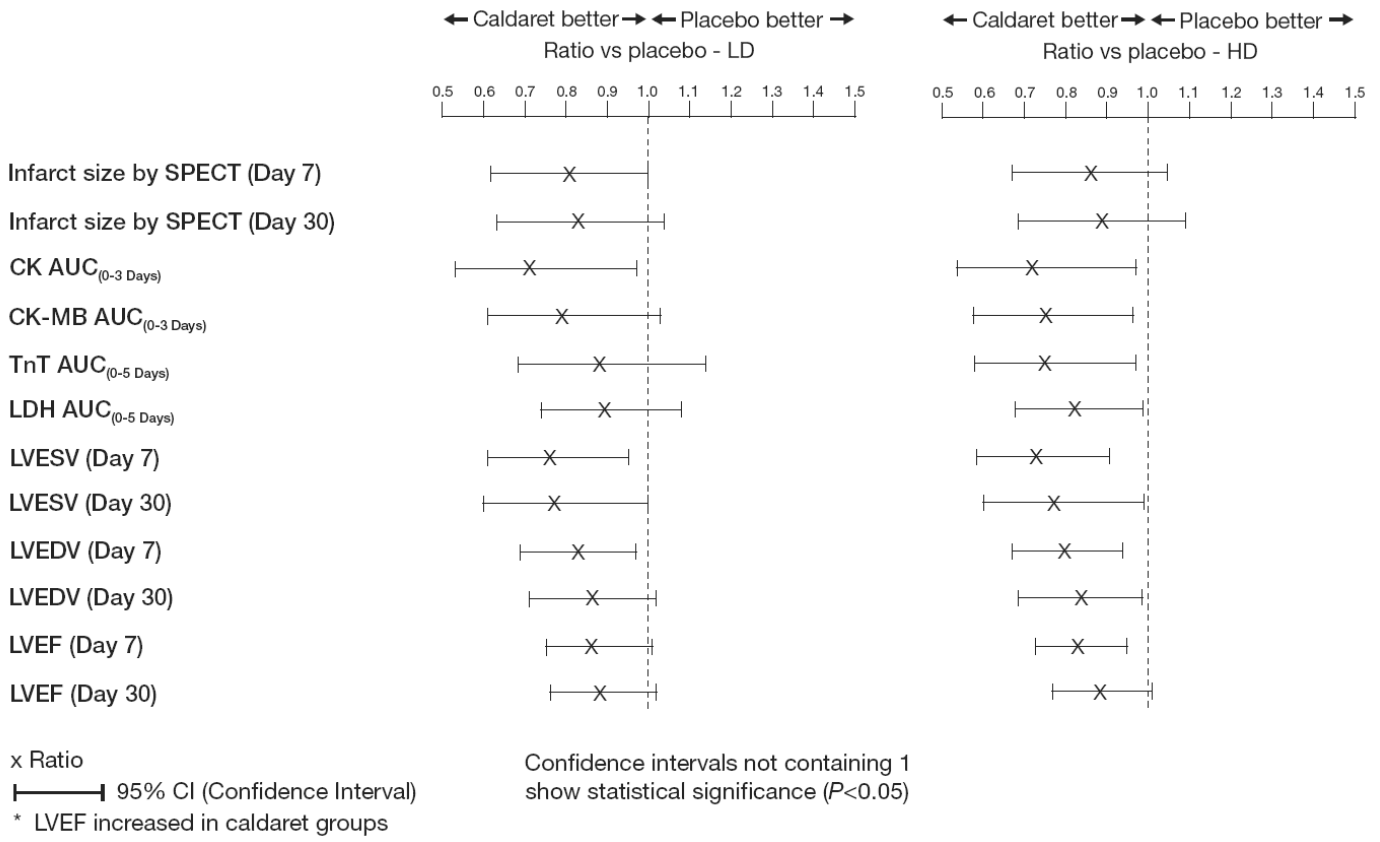


Figure 2. Study outcomes in anterior infarct patients with pre-PCI TIMI flow grade 0/1.

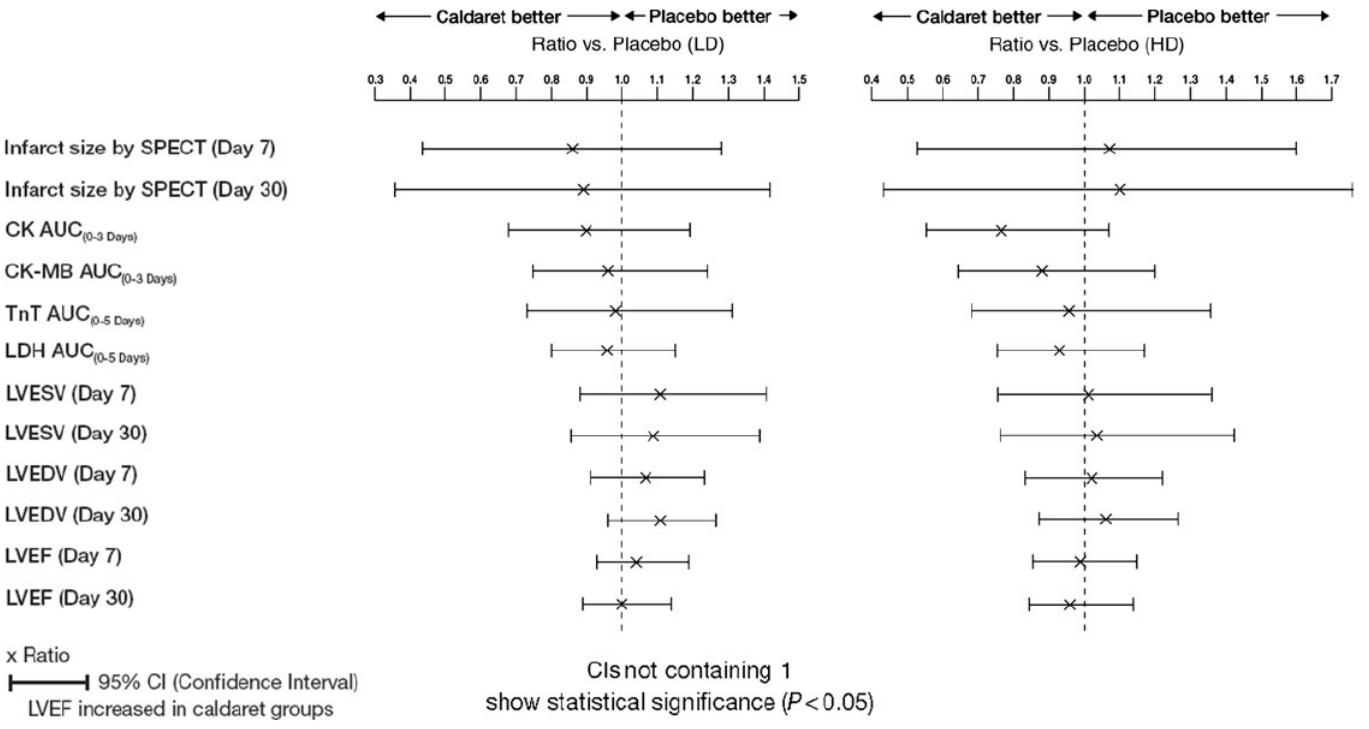


Figure 3. Study outcomes in non-anterior infarct patients with pre-PCI TIMI flow grade 0/1.

DISCUSSION

The CASTEMI study is the first human experience with caldaret in patients with large STEMI undergoing primary PCI. The most important finding of this pilot study was the safety of caldaret in patients selected for large MI by ECG criteria. Unlike reports of calcium channel blockers in this setting, this unique intracellular calcium modulator appears to be well tolerated even at HD. In theory, active prevention of intracellular calcium overload using this new molecular entity might promote more favourable cellular response to reperfusion associated with epicardial recanalization.

The limitations of this pilot study with regard to efficacy evaluations are associated with smaller treatment effects that might still be clinically meaningful (which could be missed in this relatively small cohort), the careful interpretation required of surrogate marker data, and a low overall endpoint and mortality rate even with selection of large infarctions into the study. The data showing higher rates of better pre-PCI TIMI flow in the treatment groups may also point to properties of caldaret for which there is no currently understood mechanism.

Within this negative study, the observations from the analyses controlling for infarct location showed some directional trends, possibly chance findings, in biomarkers measured. Understanding these observations requires study in an independent clinical trial.

Although the benefits of reperfusion may be limited by 'reperfusion injury',[3,4,8] the mechanism and clinical relevance of such injury remains poorly understood and multiple negative human studies have been reported,[9,17,18] including those with agents that modulate calcium homeostasis.[19] However, when administered before the onset of ischaemia, peri-operative infarct size has been reduced with Na^+/H^+ exchange inhibitors in CABG.[11]

Reperfusion injury in clinical practice has long been reported in anecdotes of epicardial reperfusion followed by rapid clinical deterioration. In animal studies, pre-treatment with a number of compounds prior to reperfusion can limit infarct size. In human patients, however, similar drugs have not shown clear benefit,[17] including in this pilot report with caldaret treatment prior to PCI. Thus, the ultimate contribution of such medical strategies for 'facilitated PCI' in STEMI to reduce infarct size remains controversial.[4,17]

CONCLUSION

With direct effect on intracellular calcium modulation, but different from calcium channel blockers, this first human pilot study demonstrates the safety of caldaret in patients with large STEMI treated with bolus and infusion of drug beginning prior to PCI. Efficacy measures were confounded by dependence on surrogates and the modest size of the cohort enrolled, with the study failing to show benefit in primary and secondary endpoints. The numerical trends in anterior infarct patients may be viewed as chance findings or hypothesis generating worthy of further study.

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CHAPTER 10

REPERFUSION INJURY IN HUMAN. A REVIEW OF CLINICAL TRIALS ON REPERFUSION INJURY INHIBITORY STRATEGIES

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ABSTRACT

The principal therapy in patients with myocardial infarction to limit infarct size is myocardial reperfusion by mechanical or pharmacological intervention. Reperfusion has been proposed to cause myocardial injury beyond that caused by the preceding ischaemia, termed "reperfusion injury" (RI). While the precise mechanism of RI is still incompletely understood, a large number of clinical studies have been performed over the past decade targeting some of the postulated mechanisms of RI. These clinical studies were based on experimental data demonstrating significant myocardial salvage. Nevertheless, clinical benefits were absent or very limited. The purpose of this review is to provide an overview of the various strategies that inhibit RI and to discuss potential mechanisms that may contribute to the discrepancy between the promising pre-clinical data and the rather disappointing results obtained from prospective clinical trials. There are numerous differences between the experimental models and clinical studies, including the fact that experimental studies typically use abrupt occlusion and reperfusion protocols in animals with previously healthy myocardium that apparently do not predict the therapeutic efficacy of novel cardioprotective agents in a clinical setting with pre-existing progressive coronary disease, intermittent coronary occlusion, and relatively late reperfusion. However, discrepancies also exist between experimental studies. Future experimental studies of reperfusion injury should use models that mimic the clinical situation more closely. Furthermore, future large clinical trials should only be performed in cases where the drug under investigation proved to reduce RI in a series of well-designed (possibly multicenter) experimental studies and in clinical trials with predefined subgroups.

INTRODUCTION

Preventing acute myocardial infarction (AMI) or limiting infarct size is critical to improve immediate and long-term outcome of patients with an acute coronary syndrome and to avoid the development of heart failure. Currently, the single established strategy to limit infarct size is early reperfusion with percutaneous coronary intervention (PCI) or thrombolytic therapy.[1] The importance of early reperfusion is not surprising as the primary insult is a decrease in oxygen supply resulting in a decrease of free energy from ATP-hydrolysis beyond a critical level required for maintaining cell processes such as ion channel function. However, despite its clear benefit, reperfusion itself has been proposed to cause irreversible myocardial damage, termed "reperfusion injury" (RI), beyond that caused by the preceding period of ischaemia, implying that optimization of reperfusion therapy could further limit infarct size.

The mechanism of RI remains incompletely understood, but may include (*i*) cytosolic and mitochondrial Ca^{2+}-overload, (ii) release of reactive oxygen species (ROS), (iii) an acute inflammatory response, and (iv) shift in substrate use.[2-8] In concert, these perturbations might pro-

duce irreversible damage to cardiomyocytes that are severely ischaemic but still salvageable at the time of reperfusion. Consequently, these pathways have been the therapeutic targets in experimental and clinical studies. Furthermore, despite restoration of epicardial coronary patency and blood flow, reperfusion after prolonged coronary occlusion is associated with secondary impairment of microcirculatory flow ("no-reflow" phenomenon), that is due to endothelial dysfunction, neutrophil plugging and oedema, but may also be aggravated by distal (micro-)embolization.[9,10]

Indirect evidence for the existence of RI stems from observations that reperfusion is associated with hypotension, temporary increase of chest pain, ST segment deviation and arrhythmias. However, direct evidence for the existence of RI stems from animal studies in which pharmacological agents administered just prior to reperfusion limit infarct size.[3,11-15] Pre-clinical studies, although sometimes equivocal, spurred a large number of clinical trials. The latter yielded mostly disappointing results and hence the existence of lethal RI in the clinical setting remains controversial.[3,11-13,16]

Table 1. List of acronyms of randomized clinical trials in alphabetical order:

ADMIRE	AmP579 Delivery for Myocardial Infarction Reduction[65]
AMISTAD	Acute Myocardial Infarction Study of Adenosine[63,64,109]
APEX-AMI	Assessment of Pexelizumab in Acute Myocardial Infarction[56]
ATTACC	Attenuation by Adenosine of Cardiac Complications[66]
CASTEMI	Caldaret (MCC-135) in ST Elevation Myocardial Infarction[39]
COMMA	Complement Inhibition in Myocardial Infarction Treated with Angioplasty[54]
COMPLY	Complement Inhibition in Myocardial Infarction Treated with Thrombolytics[55]
CORE	Collaborative Organisation for RheothRx Evaluation[47,48]
CREATE-ECLA	Clinical Trial of Reviparin and Metabolic Modulation in AMI Treatment and ECLA[79]
DATA	Diltiazem as Adjunctive Therapy to Activase[28]
ECLA	Evaluation-Estudios Clinicos Latino America[71]
ESCAMI	Evaluation of the Safety and Cardioprotective Effects of Eniporide in AMI[38]
EXPEDITION	Sodium-hydrogen Exchange Inhibition to Prevent Coronary Events in Acute Cardiac Conditions[41]
FESTIVAL	F2G in Elevated ST Infarction Evaluation[50]
GIPS	Glucose-Insulin-Potassium Study[81,82]
GUARDIAN	Guard During Ischaemia Against Necrosis[40,126]
HALT-MI	Hu23F2G anti Adhesion to Limit Cytotoxic Injury Following AMI[51]
h-SOD	Human Super-Oxide Dismutase[44]
ISIS-4	International Study of Infarct Survival[32]
LIMIT-2	Leicester Intravenous Magnesium Intervention Trial-2[31]
LIMIT-AMI	Limitation of Myocardial Infarction Following Thrombolysis in AMI[49]
MAGIC	Magnesium In Coronaries[34]
PARI-MI	Protection Against Reperfusion injury with ITF-1697 in Acute Myocardial Infarction[53]
Pol-GIK	Polish Glucose-Insulin-K^+ [80]
RAPSODY	Efficacy of a Novel P-Selectin Antagonist, rPSGL-Ig for Reperfusion Therapy in AMI[52]
REVIVAL	The Reevaluation of Intensified Venous Metabolic Support for Acute Infarct Size Limitation[83]
TAMI-9	Thrombolysis and Angioplasty in Myocardial Infarction-9[46]

The goal of the present review article is to discuss potential reasons why clinical studies have generally failed to show a beneficial effect of pharmacological interventions, despite beneficial effects reported in many experimental studies. In addition, we propose some guidelines for improving future preclinical and clinical trials. In-depth overviews of the mechanisms of RI have been published previously,[2,5,13,17] and are beyond the scope of this article.

Table 2. Randomized clinical trials on calcium homeostasis in patients with AMI

Author/year	Trial	Substrate	N	Thrombolysis	PCI	Time#	Enzymatic infarct size	Imaging	Clinical endpoints	Benefit in sub-group?
Calcium channel blockers										
Sheiban et al 1997[30]	-	Nisoldipine	36	-	100%	1,9hr	-	EF_{echo} ↑	-	
Theroux et al 1998[28*]	DATA	Diltiazem	59	100%	-	2,7hr	↔	EF_{SPECT} ↔	MACE ↓	
Pizzetti et al 2001[29]	-	Diltiazem	90	100%	-	2,2hr	↓	EF_{echo} ↑	↔	
Magnesium										
Woods et al 1992[31]	LIMIT-2	$MgSO_4$	2.316	36%	-	3hr	↔	-	Mortality ↓	
ISIS-4 1995[32¥]	ISIS-4	$MgSO_4$	58.050	70%	-	8hr	-	-	MACE ↔	
Santoro et al 2000[33§]	-	$MgSO_4$	150	-	100%	3,5hr	↔	EF_{echo} ↔	↔	
MAGIC 2002[34†]	MAGIC	$MgSO_4$	6.213	19%	12%	n.r.	-	-	Mortality ↔	
NHE-inhibitors										
Rupprecht et al 2000[37]	-	Cariporide	100	-	100%	3,8hr	CK(MB) ↔(↓)	EF_{angio} ↑	Mortality ↔	
Zeymer et al 2001[38]	ESCAMI	Eniporide	1.389	61%	38%	3,1hr	↔	-	↔	Time† >4hrs
Bär et al 2004[39‡]	CASTEMI	Caldaret	247	-	100%	3,3hr	-	EF_{SPECT} ↔	↔	Anterior MI

PCI = percutaneous coronary intervention; # approximate time from onset of symptoms to treatment; hr = hours; CK(-MB) = creatine kinase (-myocardial band isoenzyme subfraction); SPECT = single-photon emission computed tomography; MACE = major adverse cardiac events (death, recurrent myocardial infarction, recurrent ischaemia); ‡: TIMI 0-1 only; n.r. = not reported.
All substrates infused before the onset of reperfusion therapy, except for ¥: Bolus $MgSO_4$ started after lytic phase, §: Bolus and infusion started before or after PCI; †: in 5% of all patients infusion started after reperfusion therapy. All substrates administered intra-venously except for *: intra-venous infusion for 48hr followed by oral treatment for 4wks
↑ significantly increased; ↔ no significant effect; ↓ significantly decreased.

Ca^{2+}-overload (Table 2)

Intracellular Ca^{2+} increases during prolonged ischaemia and subsequent reperfusion. Ca^{2+}-overload during ischaemia is partially due to activation of the Na^+/Ca^{2+}-exchanger and opening of L-type Ca^{2+}-channels, in conjunction with inhibition of sarcolemmal and sarcoplasmic reticular Ca^{2+}-pumps.[13] During reperfusion, the Na+/H+-exchanger is activated to restore intracellular pH. However, the extrusion of H^+ initiates a net influx of Na^+ into the cardiomyo-

cyte, which via the Na^+/Ca^{2+}-exchanger leads to further increase in Ca^{2+}-influx during early reperfusion.[13] The Ca^{2+}-overloaded myocytes enter into a state of hypercontracture when exposed to oxygen and energy, after reperfusion.[13,14,18] Furthermore, Ca^{2+}-overload induces protease activation, gap-junction dysfunction and membrane rupture that cumulatively contribute to cell death.[19]

Ca^{2+}-channel blockers and magnesium

Blockade of the L-type Ca^{2+}-channel can prevent Ca^{2+}-overload during prolonged ischaemia and reperfusion.[20] In experimental models of coronary occlusion, Ca^{2+}-antagonists limit irreversible myocardial damage and reduce the degree of stunning, provided these agents are administered *prior* to ischaemia.[21,22] $MgSO_4$ also possesses Ca^{2+}-channel blocking properties, which may aid in preventing Ca^{2+}-overload during reperfusion[20] and may protect against reactive oxygen species.[23] Interestingly, intracellular Mg^{2+} levels are depressed during AMI,[24] while supplemental Mg^{2+} has been reported to reduce infarct size when administered prior to reperfusion.[25,26]

Clinical trials. Clinical evidence regarding the benefit of Ca^{2+}-channel blockers in the setting of AMI remains inconclusive when treated with Ca^{2+}-channel blockers on top of reperfusion therapy, despite their beneficial effects in reversible ischaemic syndromes.[27] Two of three small pilot studies showed improvement of left ventricular function (echocardiography)(Table 2).[21,22,28-30] The DATA trial showed improved clinical outcome (n=59), despite a lack of efficacy of diltiazem on infarct size or left ventricular function.[24] There is no indication for Ca^{2+}-channel blockers as an adjunct to reperfusion therapy as large randomized trials are lacking. Trials on the use of $MgSO_4$ (an endogenous Ca^{2+}-antagonist) in patients with AMI showed similarly negative results in over 60.000 patients (Table 2).[31-34]

Na^+/H^+ exchange inhibitors

Experimental studies have demonstrated marked limitation of infarct size when NHE-inhibitors are administered prior to ischaemia.[35] However the efficacy of NHE-inhibitors administered just prior to reperfusion remains controversial.[36]

Clinical trials. Except for a pilot study in 100 patients with cariporide,[37] NHE-inhibitors generally failed to demonstrate any benefit on infarct size or clinical outcome when given *after* onset of ischaemia in the setting of AMI (ESCAMI trial (n=1389) with eniporide and CASTEMI trial (n=247) with caldaret (Table 2).[38,39] However, when the NHE-inhibitor cariporide was given *before* ischaemia in patients undergoing CABG, a reduction in peri-operative cardiac enzyme release was observed in the GUARDIAN CABG subgroup[40] and the large EXPEDITION study (n=5761).[41] This was associated with an improvement in outcome in the GUARDIAN CABG subgroup, whereas the EXPEDITION trial showed an overall increase in mortality, and inexplicably, strokes.[41] Nevertheless, GUARDIAN and EXPEDITION support the concept that that irreversible myocardial damage is reduced by NHE inhibitors administered *prior* to the onset of ischaemia.

Table 3. Randomized clinical trials on anti-inflammatory agents in patients with AMI

Author/year	Trial	Substrate	N	Thrombolysis	PCI	Time#	Enzymatic infarct size	Imaging	Clinical endpoints	Benefit in sub-group?
Anti-reactive oxygen species										
Flaherty et al 1994[44]	h-SOD	h-SOD	120	-	100%	4.1hr	-	EF_{angio} ↔	Mortality ↔	
Tsujita et al 2004[45 †]	-	Edaravone	80	-	100%	3,3hr	↓	EF_{echo} ↔	-	
Endothelial preservation and PMN inhibitors										
Wall et al 1994[46]	TAMI-9	Fluosol	430	100%	-	n.r.	-	$EF_{Thallium}$ ↔	↔	
Schaer et al 1996[47]	CORE-Pilot	RheothRx	114	100%	-	2,8hr	-	EF_{MIBI} ↑	↔	
CORE Group 1997[48]	CORE	RheothRx	2.948	100%	-	3.5hr	-	EF_{SPECT} ↔	Mortality/ CHF ↔	
Baran et al 2001[49]	LIMIT-AMI	RhuMab CD 18	394	100%	-	3,4hr	↔	EF_{SPECT} ↔	↔	
Rusnak et al 2001[50]	FESTIVAL	Hu23F2G	60	-	100%	n.r.	-	EF_{SPECT} ↔	↔	
Faxon et al 2002[51]	HALT-MI	Hu23F2G	420	-	100%	3.8hr	↔	EF_{SPECT} ↔	↔	
Tanguay et al 2003[52 @]	RAPSODY	rPSGL-Ig	598	100%	-	< 6hr	-	EF_{SPECT} ↔	↔	
Dirksen et al 200453	PARI-MI	ITF-1697	393	-	100%	4.1hr	↔		↔	
Anti-complement										
Granger et al 2003[54]	COMMA	Pexelizumab	814	-	100%	3,2hr	↔	-	Overall ↔ Mortality ↓[§]	
Mahaffey et al 2003[55]	COMPLY	Pexelizumab	920	100%	-	2,8hr	↔	-	↔	
Armstrong et al 2006[56]	APEX-AMI	Pexelizumab	5745	100%	-	n.r.	-	-	↔	
Adenosine										
Mahaffey et al 1999[63]	AMISTAD	Adenosine+lido	236	100%	-	2,9hr	↔	EF_{SPECT} ↔	↔	Anterior MI
Kopecky et al 2003[65]	ADMIRE	AmP579	311	-	100%	n.r.	-	EF_{SPECT} ↔	n.r.	Anterior MI
Quintana et al 2003[66]	ATTACC	Adenosine	608	100%	-	3,3hr	-	EF_{echo} ↔	Mortality/ CHF ↔	
Marzilli et al 2000[67]	-	Adenosine[F]	54	-	100%	1,9hr	↔	EF_{echo} ↑	Mortality and MI ↓	
Ross et al 2005[64]	AMISTAD-II	Adenosine+lido	2.118	58%	40%	3,3hr	↔	EF_{SPECT} ↔	Mortality/ CHF ↔	High-dose

PCI = percutaneous coronary intervention; #: approximate time from onset of symptoms to treatment; hr = hours; †: TIMI 0-1 only; lido = lidocaine; SPECT = single-photon emission computed tomography; CHF: congestive heart failure; n.r. = not reported; @: Abstract only. §: No benefit in infarct size reduction or event free survival, however unexplained significant reduction of all cause mortality.

All substrates administered before the onset of reperfusion therapy and all substrates administered intra-venously except [F]: intra-coronary.

↑ significantly increased; ↔ no significant effect; ↓ significantly decreased.

The results of these trials are consistent with animal studies that show that NHE-inhibitors are principally only effective when given *before* ischaemia.

Anti-inflammatory strategies (Table 3)

Key events in the inflammatory response to ischaemia-reperfusion are the production of reactive oxygen species (ROS), complement activation, neutrophil activation and endothelial dysfunction. These processes may produce irreversible cardiomyocyte damage directly, but also indirectly via myocardial oedema and capillary plugging by polymorphonuclear cells (PMN) causing "no-reflow".[42,43]

Clinical trials. Studies using anti-inflammatory strategies have generally yielded disappointing results and will not be discussed in detail in this manuscript. These clinical trials are summarized in Table 3. Thus, pilot trials with anti-oxidants (a recombinant human SOD and edaravone, a ROS scavenger) in the setting of primary PCI for AMI failed to demonstrate efficacy (Table 3).[44,45] In addition, despite equivocal experimental data regarding a causal role of PMNs in lethal RI, clinical trials were initiated using drugs that inhibit PMN tethering and activation [46-51], inhibit PMN adhesion molecules,[52] or preserve endothelial function (Table 3).[53] Disappointing results were reported in these 8 (predominantly phase II) clinical trials with agents that inhibit PMN activation and endothelial dysfunction.[46-53] Finally, complement inhibition with a monoclonal antibody (anti-C5), pexelizumab, was investigated in patients with AMI in the COMMA,[54] the COMPLY[55] and the APEX-AMI trial.[56] All three trials failed to demonstrate a limitation of infarct-size (total CK-MB) or composite clinical endpoint. However, the COMMA-trial did show an unexplained decrease in overall mortality with pexelizumab (Table 3).[54]

Adenosine

Adenosine exerts a multitude of actions that can protect the myocardium against RI, including anti-ischaemic effects via pharmacological preconditioning, inhibition of PMN-activation and ROS formation, anti-inflammatory properties, preservation of endothelium and microvascular flow.[57] Adenosine has demonstrated marked cardioprotection in animal studies, when administered *before* ischaemia. Conversely, administration *after* the onset of ischaemia has yielded variable results,[58-60] that may in part be due to co-administration of lidocaine[59-61] or collateral flow level.[50]

Clinical trials. Following a promising non-randomized pilot trial (n=45),[62] the AMISTAD-I[63] and II[64] trials investigated the effect of adenosine in combination with lidocaine as an adjunct to reperfusion therapy in patients with AMI. The first AMISTAD trial included 236 patients who were randomly assigned to either placebo or adenosine with lidocaine on top of thrombolysis for AMI. Although adenosine treatment did not modify overall infarct size (SPECT), the anterior infarct subgroup showed significant reduction. Consequently, the AMISTAD-II was conducted exclusively in patients (n=2.084) with anterior AMI. Although adenosine did not show an

overall benefit, the authors reported a trend towards a modest limitation in infarct size in the high-dose adenosine subgroup compared to placebo (Table 3).[64] The ADMIRE (n=608; reperfusion by thrombolysis) and the ATTACC (n=311 with anterior MI; reperfusion by PCI) trials also failed to observe beneficial effects of adenosine treatment on infarct size or clinical outcome, although a trend towards greater myocardial salvage assessed by SPECT was apparent in the ADMIRE trial (Table 3).[65,66]

The anti-inflammatory and coronary vasodilator actions of adenosine may limit no-reflow following reperfusion and hence reduce secondary myocardial ischaemia.[58] A pilot study (n=54) investigated the effects of intracoronary adenosine administered just before reperfusion in patients with AMI.[67] No-reflow was observed in 1 patient in the adenosine group and in 7 patients in the placebo group ($p<0.05$), which was associated with significant improvement in ventricular function (echocardiography) and clinical improvement.

Taken together, clinical trials with adenosine as an adjunct to reperfusion therapy have failed to show a significant beneficial effect. However, the potential of adenosine to improve microvascular function and reduce infarct size when administered before the onset of ischaemia (similar to the experimental studies), e.g. in the setting of CABG, deserves further investigation.[68]

Metabolic interventions: glucose-insulin-potassium (table 4)

The concept of glucose-insulin-K^+-therapy (GIK) was introduced 44 years ago by Sodi-Pallares and thought to be protective by stabilization of the membrane.[69] From observations that glucose is a preferential energy source during ischaemia and reperfusion the concept emerged that GIK therapy may limit infarct size.[70-73] Additionally, GIK decreases circulating levels of free fatty acids and myocardial free fatty acids uptake, possibly limiting toxic concentrations in ischaemic myocardium.[74] Finally, insulin can exert anti-RI effects by activation of Akt and p70s6 kinases.[75] GIK has been shown to be protective against RI following AMI in the majority of animal studies, also when administered after the onset of ischaemia.[75-78]

Clinical trials. Meta-analysis of trials from the pre-thrombolytic era suggests therapeutic benefit of GIK treatment.[72] Six recent trials also showed some benefit of GIK, but only in specific subgroups (Table 4).[71,79-82] In the ECLA study (n=407) GIK therapy, starting 10-11 hours after onset of symptoms, improved clinical outcome in the reperfused patients (62% of total study population).[66] In the CREATE-ECLA-trial (n=20.000; reperfusion therapy in 83%), GIK treatment failed to improve 30-days clinical outcome although there was a trend towards improved clinical outcome in patients undergoing reperfusion therapy by PCI (9% of all patients).[79] Conversely, the Pol-GIK-trial in a low-risk AMI patient population (Killip I-II) was terminated prematurely because of an increase in mortality in GIK-treated patients.[80] The REVIVAL study evaluated GIK treatment started within 10 hours of start of symptoms in 312 patients undergoing reperfusion therapy. No infarct size reduction as assessed by SPECT was shown, although GIK-treated patients with diabetes (n=35) showed improved myocardial salvage.[83]

Table 4. Randomized clinical trials with glucose-insulin-potassium (GIK) in patients with AMI

Author/year	Trial	N	Thrombolysis	PCI	Time#	Enzymatic infarct size	Clinical endpoints	Benefit in sub-group?
Díaz et al 1998[71]	ECLA	407	59%	3%	10,5hr	n.r.	MACE* ↓	Reperfused patients
CREATE-ECLA Group 2005[79]	CREATE-ECLA	20.201	74%	9%	4.7hr	n.r.	MACE§ ↔	
Ceremuzynski et al 1999[80 ¥]	Pol-GIK	954	57-60%	-	< 24hr	↔	Mortality ↑	
van der Horst et al 2003[81]	GIPS	940	-	100%	n.r.	n.r.	Mortality ↔	Killip class I
Timmer et al 2006[82]	GIPS-II ┗	889	12%	88%	3.7	↔	Mortality ↔	
Pache et al 2004[83]	REVIVAL	312	4%	89%	10hr	n.r.	Mortality ↔	Diabetes

PCI = percutaneous coronary intervention; #: approximate time from onset of symptoms to treatment; hr = hours; *: death, nonfatal congestive heart failure, and nonfatal ventricular fibrillation; ¥: Terminated prematurely, because of an increase in mortality in GIK treated patients; §: MACE: death, recurrent-MI, cardiogenic shock, cardiac arrest; ┗ only patients with Killip class < II included.
All substrates administered intra-venously.
↑ significantly increased; ↔ no significant effect; ↓ significantly decreased.

Recent studies performed in the Netherlands yielded similar results for GIK treatment on top of primary PCI in the setting of AMI (Table 4).[81,82] Analysis of the total study population in the GIPS-I (n=904) and patients without clinical evidence of heart failure in the GIPS-II (n=889) failed to demonstrate a reduction in 30-days mortality or limitation in enzymatic infarct size, despite significant reduction in the subgroup with patients without evidence of heart failure in the GIPS-I.[81,82]

GIK has also been investigated as adjunctive therapy to CABG.[84] A review of 91 studies indicates a benefit of insulin or GIK in 74 of these studies.[85] Despite the reports in which GIK treatment suggested additive benefit on clinical outcome and peri-operative infarct size, GIK is currently not used routinely in clinical practice because of a lack of unequivocally positive results.[85]

Miscellaneous

Various other cardioprotective agents, such as trimetazidine, angiotensin converting enzyme (ACE)-inhibitors and nicorandil, have been evaluated in the setting of AMI. None of these trials showed satisfactory proof of infarct size reduction in adequately sized trials (Table 5).[86-90] Consequently none of these agents is currently being used in AMI, and await evaluation in larger trials.

Table 5. Randomized clinical trials with miscellaneous agents in patients with AMI

Author/year	Trial	Substrate	N	Thrombolysis	PCI	Time#	Enzymatic infarct size	Imaging	Clinical endpoints
EMIP-FR Group 2000[86]	EMIP-FR	Trimetazidine	19.725	56%	-	< 24hr	n.r.	-	Mortality ↔
Kurz et al 2001[87 ¥]	-	Enalaprilat	22	-	100%	< 5hr	↔	EF_{angio} ↔	-
Sakata et al 1997[88 ¥]	-	Nicorandil	20	-	100%	n.r.	n.r.	EF_{echo} ↑	n.r
Ito et al 1999[89 †]	-	Nicorandil	81	-	100%	< 12hr	n.r.	EF_{echo} ↑	AE[§] ↓
Ono et al 2004[90]	-	Nicorandil	58	-	100%	< 6hr	n.r.	EF_{angio} ↑	↔

PCI = percutaneous coronary intervention; #: approximate time from onset of symptoms to treatment; hr = hours; *: death, nonfatal congestive heart failure, and nonfatal ventricular fibrillation; n.r. = not reported; §: AE: Adverse events: congestive heart failure, ventricular arrhythmias or pericardial effusion;.

All substrates administered intra-venously, except ¥: intra-coronary; †: anterior MI only.

↑ significantly increased; ↔ no significant effect; ↓ significantly decreased.

Mechanical modulation of reperfusion

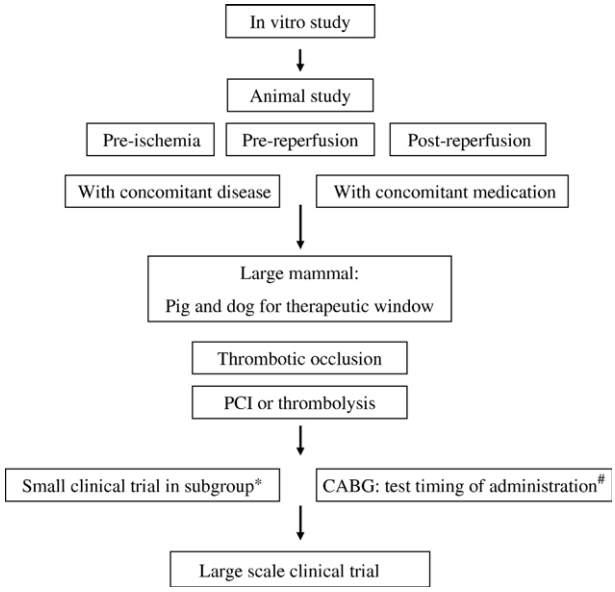
Gradual reinstitution of blood flow during reperfusion has been shown to limit RI in the setting of experimental ischaemia-reperfusion.[91] Recently, this phenomenon was extended when Zhao *et al* showed that infarct size in dogs was reduced by a sequence of brief re-occlusions following prolonged ischaemia.[92] This phenomenon, termed "postconditioning", has been confirmed in several other animal species,[93,94] and probably involves a reduced inflammation and oxidative stress,[92] and the activation of reperfusion injury salvage kinase pathways[93,94] resulting in reduced mitochondrial permeability.[95]

Clinical trials. Staat *et al* investigated the effect of postconditioning in 30 patients with AMI and reported limitation of enzyme release and improvement of myocardial perfusion [95], supporting the concept that lethal myocardial RI in humans may be limited by (mechanical) intervention.[95] However, these promising initial results await confirmation in large trials.

WHAT IS THE CAUSE OF THE PREDOMINANTLY NEGATIVE CLINICAL TRIALS?

A reconciliation of the discordance between the often positive findings in pre-clinical studies and the predominantly negative clinical trials requires a careful assessment of differences in methodology and biology between experimental and clinical studies.

Figure 1. Flow-chart for suggested development of new reperfusion inhibitory drugs



*Prospective patient stratification with or without all confoundingfactors as mentioned in Table 6, e.g.: TIMI flow grade 0–1, pre-infarct angina, concomitant medication, young, anterior wall infarction, etc;

administration of agent before the onset of ischemia, during ischemiabut minutes before reperfusion and at reperfusion.

Co-morbid conditions

Concomitant disease

In contrast to the majority of pre-clinical studies, in which healthy young animals are typically employed, ischaemic heart disease and myocardial infarction in humans is principally a disease of the middle-aged and elderly. The co-morbid conditions leading to ischaemic heart disease (e.g. atherosclerosis, hypercholesterolemia, hypertension and diabetes), advanced age, and impaired nutritional status and that are typically absent in preclinical studies, may blunt the efficacy of cardioprotective therapies.[53,96,97]

Preconditioning

The hearts of healthy animals in the pre-clinical studies have not been exposed to ischaemia prior to infarction. In contrast, brief ischaemic episodes and gradual occlusion preceding myocardial infarction, as occurs clinically during episodes of pre-infarct angina pectoris,[98] may modulate the protective effects of pharmaco-therapy by inducing 'ischaemic preconditioning'.[11] Conversely, subsets of patients may have become tolerant to preconditioning due to repeated

ischaemic episodes in which pharmacological protection may provide an important contribution to cardioprotection.[99]

Concomitant medication

The concomitant medication used during routine clinical practice, and which is typically absent in experimental studies, may influence the effectiveness of agents directed against RI.[49,53] Current reperfusion therapy of acute myocardial infarction involves treatment with vasodilators (including nitroglycerin, opiates, nitroprusside or dobutamine), medication with specific effects on thrombus formation, coagulation and platelet activation (heparin, aspirin, clopidogrel and GPIIb/IIIa receptor blockers), substitution of lost electrolytes and diuretics in case of increased filling pressures. It remains unclear whether these drugs have an effect on RI or modify the cardioprotective effects of the drug under investigation, but heparin and GPIIb/IIIa receptor blockers could influence the effect of agents RI inhibitory drugs on adherence and extravasation of PMNs via modulation of chemotactic cytokines such as CD11/CD18 and ICAM-1 receptors.[100] Conversely, sub-analyses of patients treated with or without GPIIb/IIIa receptor blockers in the PARI-MI and LIMIT-AMI trial did not reveal a different effect of the reperfusion inhibitory substrate interfering with this same pathway of PMN accumulation, adhesion and activation.[49,53] Nevertheless observations that GPIIb/IIIa receptor blockers improved microvascular flow may suggest that GPIIb/IIIa receptor blockers influence inflammation.[101] Similarly, the effect of agents such as NHE-blockers and adenosine on RI could be superseded by the effects of standard concomitant medication in patients with coronary artery disease influencing the cellular electrolyte homeostasis, such as beta-blockers, Ca^{2+}-blockers and ACE-inhibitors.[102,103] Finally, it should be noted that many patients that encounter an AMI are already treated for hypercholesterolemia and hypertension. Recently, it was demonstrated that statin treatment started before ischaemia reduced infarct size in a rat ischaemia-reperfusion model.[104] Several experimental studies showed a possible effect of widely used anti-hypertensive and/or anti-anginal medication on RI, such as ACE-inhibitors and Ca^{2+}-channel blockers.

In conclusion, co-morbid conditions are likely to modulate the efficacy of new cardioprotective drugs under investigation, but these are typically not taken into account in experimental studies. Future experimental studies should take into account these co-morbid conditions.

Determinants of infarct size

The main determinants of infarct size include the area at risk, the severity of ischaemia, the duration of ischaemia, and the mode of reperfusion.[105] In contrast to the clinical setting, these factors can either be controlled or accurately determined in the experimental models.

Location and size of the area at risk

In contrast to preclinical studies in which infarct size is related to the anatomical area at risk, clinical studies typically express infarct size as a percent of the left ventricle, resulting

in greater infarct size variability. Furthermore, animal studies primarily examine anterior infarction, while the majority of clinical trials included both patients with anterior as well as inferior wall infarctions. Interestingly, there are some trials indicating beneficial effects of a reperfusion inhibitory drug in patients with anterior wall infarction.[37,39,63] The explanation for this localized feature is unknown and may be related to anatomical and biological differences, including area at risk size and degree of collateral flow.

Severity of ischaemia

The severity of ischaemia is dependent on both the degree of residual antegrade flow and collateral flow.[106,107] In animal studies total coronary occlusions are typically used. In contrast, in clinical studies coronary obstruction is variable, either gradual or abrupt, intermittent or constant, partial or complete, thereby increasing infarct size variability. In addition, collateral blood flow in individual humans demonstrates a high degree of variability (e.g. young patient versus an older patient with chronic coronary artery disease),[108] but is rarely determined in clinical studies, which will increase infarct size variability.

Duration of ischaemia

The majority of animal studies use a prospectively determined duration of ischaemia ranging from 30-90 minutes. In the clinical setting, the exact duration of ischaemia and the onset of reperfusion are difficult to establish, particularly in thrombolytic trials, but the duration of ischaemia is typically much longer (>2 hours from onset of symptoms to reperfusion, see Tables 2-5) compared to the laboratory setting. This may result in extensive *ischaemic* damage, leaving less room for RI limiting strategies.[53,96] Indeed, this is supported by clinical event reduction in patients treated early (within 3.17 hours) in the AMISTAD-II trial.[109] However, other clinical studies could not confirm such a benefit in the subgroup of patients with re-established flow within two hours of symptom onset.[49,53]

Mode of occlusion and reperfusion

In experimental studies, ischaemia-reperfusion is typically produced by a mechanically induced abrupt and total coronary occlusion and reperfusion. This contrasts with the more unpredictable coronary occlusion in the clinical setting that may be either gradual or acute. Reperfusion by thrombolysis is gradual and intermittent[33] and may result in incomplete reperfusion due to persistence of the coronary stenosis.[110,111] Importantly, the repetitive-intermittent ischaemia caused by both thrombolysis (incomplete reperfusion) and PCI (balloon dilatation and stent implantation) may induce postconditioning, a feature that is typically avoided in experimental studies[112] In support of this concept, a study in which coronary occlusion and reperfusion was produced by formation and lysis of a thrombus failed to show cardioprotection by the drug under investigation.[42]

In conclusion, several determinants of infarct size have been identified in the experimental setting and are typically controlled or measured and accounted for. In contrast, these determinants are frequently overlooked in clinical studies of AMI, thereby acting as confounders and hampering detection of a protective effect by the drug under investigation.

Treatment related aspects

Distal embolization

Impaired post-procedural perfusion could be, at least in part, the result of embolization of plaque debris and thrombus into the distal microvasculature rather than of the result RI.[96,113-115] Macro- and micro-embolization are both associated with reduced myocardial reperfusion, more extensive myocardial damage and a poor prognosis.[115,116] This embolization can occur spontaneously or as a result of intracoronary manipulation (wires, balloon dilatation and stent implantation). The plaque and thrombus content is washed out into the distal microvasculature[114,117] in 10-15% of patients,[115,116,118] where they mechanically "plug" the microvasculature, but can also produce spasm and local inflammation.[113]

To prevent plaque and thrombus wash-out several distal protection devices are currently under evaluation, two of which did not show improvement in microvascular flow, infarct size or event-free survival.[119,120]

Timing of drug administration

Preclinical studies demonstrated that several drugs are beneficial when given before the onset of ischaemia but do not consistently exhibit a beneficial effect when given just prior to *reperfusion*.[12,42,96,121] Clinical trials suggest a similar trend as the majority of drugs administered in the setting of an AMI before the onset of reperfusion failed to limit infarct size or improve outcome (Tables 2-5), compared to administration prior to *ischaemia,* in the setting of CABG. Thus, patients *pretreated* before CABG showed reduced peri-operative MI,[40,41,122] suggesting that these drugs may simply not be effective against RI in the setting of AMI.

Does medication reach the jeopardized myocardium in sufficiently concentrations

Another explanation for the inconsistent results, is that drugs may not reach the area at risk in sufficiently high concentrations prior to reperfusion. This concept is supported by pre-clinical studies with NHE-inhibitors, reporting that higher doses are required with delayed administration[123] while resulting in only modest effects.[124,125] The importance of sufficient dosing is also suggested by the observations that benefits occurred only in the high dose groups in several clinical studies.[39,64,126]

In conclusion, there is evidence from CABG studies that cardioprotection in humans does occur when pharmacological agents are administered prior to ischaemia. Furthermore, there is some experimental evidence that a sufficiently high concentration during the first few minutes after

reperfusion can result in infarct size limitation. The inability to meet these requirements might contribute to the failure to observe RI limitation in the majority of clinical studies.

Methodology and study design

Choice of endpoints

The primary endpoint of the majority of animal experiments is infarct size, expressed as a percentage of area at risk.[12,106,127] Clinical endpoints, such as mortality, would require unacceptably large numbers of animals. Histochemical staining with tetrazolium salts has been thoroughly validated, and remains the golden standard. In clinical trials the primary endpoints often include mortality, recurrent ischaemia, congestive heart failure and stroke. However, reperfusion therapy (PCI and thrombolysis) has reduced mortality after AMI to low levels (4-6%),[128] making further significant reductions by adjunctive agents difficult to achieve. Although all methods to assess infarct size, including serum markers and imaging modalities, have their limitations,[127] in phase II "proof of concept" trials infarct size is considered the most appropriate surrogate end-point for evaluating the efficacy of RI-inhibitory drugs.

Biases

A 'publication bias' may also contribute to the discrepancy between the weight of preclinical versus clinical data. Thus, negative trial results are obviously less exciting and often more difficult to get published. Similarly, there may be bias in the evaluation of available experimental data before starting a clinical trial.[42] Thus, clinical trials were often initiated even though drugs showed inconsistent results in experimental animal studies.[12]

SUMMARY, CONCLUSION AND FUTURE PERSPECTIVES

Experimental observations that drugs are capable of limiting infarct size when administered just prior to or at the onset of reperfusion have prompted a large number of clinical trials investigating the therapeutic potential of several agents against RI in the setting of AMI, that generally have been disappointing. Potential explanations for the discrepant findings between preclinical and clinical studies are summarized in Table 6. Future studies into novel drugs that have shown promise in the experimental setting, including Na^+/Ca^{2+}-exchange inhibitors, protease inhibitors, and cyclic GMP mimetics, should take these factors into account.

Figure 1 depicts a flow-chart from pre-clinical studies to large randomized double-blind clinical trials that is recommended for future evaluation of RI limiting strategies. For example, timing of drug administration, animal species (species with or without collaterals) and mode of occlusion and reperfusion should be rationally chosen.[129] Furthermore, animal experiments should consider the impact of co-morbid conditions and co-medication on the cardioprotec-

Table 6. Major differences between animal versus clinical trials.

	Animal experiments	Clinical trials
Co-morbid conditions		
Concomitant disease		
Myocardium	Naïve and young	Atherosclerosis and senescence
Endothelium	Naïve	Atherosclerosis and endothelial dysfunction
Concomitant disease	Rare	Hypertension, diabetes mellitus, hypercholesterolemia, LVH
Preconditioning/pre-infarct angina	No	Yes
Concomitant medication		
Pre-procedure	No	Beta-blockers, nitrates, statins, ACE-inhibitors, Ca2+ blockers
Peri-procedural	Rare	Aspirin, heparine, GP IIb/IIIa receptor blockers, clopidogrel
Determinants of infarct size		
Location and size of area at risk		
Area at risk	Exact	Rarely determined
Location of infarct	Mainly anterior wall	Variable
Severity of ischaemia		
Degree of antegrade flow	Abrupt and constant	Gradual or abrupt; intermittent or constant
TIMI flow grade	0	0-2
Degree of collateral flow	Variable, species dependent	Variable, dependent on extent of disease
Determination of collateral flow	Always determined	Rarely determined
Duration of ischaemia		
Determination	Exact	Uncertain
Time of occlusion	15-90 minutes	> 2 hours (range 1.9-24 hours)
Mode of occlusion		
Mode	Mechanical clamping	Atherosclerotic and/or thrombotic
Completeness	100%	Incomplete or complete
Onset	Abrupt	Gradual or abrupt
Mode of reperfusion		
Mode	Release of mechanical clamp	PCI or thrombolysis
Completeness	100%	Incomplete or complete
Onset	Abrupt	Gradual with thrombolysis, abrupt with PCI
Postconditioning	No	Yes (especially with PCI)
Treatment related aspects		
Distal embolization	No	Often, in PCI at least 10-15%
Timing of drug administration		
Related to ischaemia	Before or after onset of ischaemia	After onset of ischaemia (except CABG)
Related to reperfusion	Before onset of reperfusion	Before or after uncertain reperfusion
Methodology and study design		
Choice of endpoints	Infarct size	Clinical follow-up, infarct size, (micro-)vascular perfusion
Infarct size	TTC staining	Imaging (SPECT, MRI, echocardiography) and serum markers
Functional	Rare	Imaging (SPECT, MRI, echocardiography)
Microvascular perfusion	No	Myocardial blush grade, ST-segment resolution
Study design		
Randomized	Rare	The majority
Blinded	Rare	The majority
Multicenter	Rare	The majority

TIMI = Thrombolysis In Myocardial Infarction; PCI = percutaneous coronary intervention; TTC = tryphenyltetrazolium chloride; LVH = left ventricular hypertrophy; MI = myocardial infarction; CHF = congestive heart failure; SPECT = single-photon emission computed tomography; MRI = magnetic resonance imaging; CABG = coronary artery bypass graft.

tive efficacy of novel agents.[12] The occlusion of arteries should mimic thrombotic occlusion in contrast to arterial clamping, and reperfusion should mimic thrombolysis or PCI.

To prevent inappropriate clinical trials, an expert Working Group recently proposed that clinical trials with new agents should be initiated only after the therapy proves to be reproducibly effective in multiple animal models, ideally performed in a randomized, blinded and multicenter approach analogous to clinical trials.[12,121] Only then clinical testing should be started, initially focusing on predefined subgroups for proof of concept, before conducting a large scale clinical trial. First, studies should be performed in patients undergoing CABG to allow detection of cardioprotection by drugs when administered prior to ischaemia. Subsequently, studies should be considered in subgroups of AMI patients that are more similar to the animal experimental, e.g. patients with naïve vessels (young, no previous cardiac history, without pre-infarct angina), anterior wall infarction, and a totally occluded infarct-related artery and no co-medication at presentation. Large scale clinical trials should only be performed after such initial trials turn out positive.

In conclusion, the evidence presented in this review suggests that future studies pertaining to limitation of ischaemia-reperfusion injury in patients with AMI have a very low likelihood of success. However, the limitation of myocardial infarct size reported in experimental studies when administered *prior* to ischaemia and reperfusion warrants further investigation into this field, taking into account the lessons taken from the animal experimental and clinical studies as presented in this review article.

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CHAPTER 11

SUMMARY, CONCLUSIONS & FUTURE DIRECTIONS

This thesis describes several aspects of pathophysiology, diagnosis and treatment of acute myocardial infarction (AMI). Specifically, its aim was to:

1) Enhance our insight into the *pathophysiology* of plaque stability.
2) Evaluate the accuracy of the electrocardiogram for the *diagnosis* of AMI.
3) Improve *treatment* with primary percutaneous coronary intervention by the use of the transradial approach and drug-eluting stents.
4) Reduce the adverse *sequelae* of reperfusion therapy in AMI, i.e. limit purported reperfusion injury in patients with AMI; and finally, review clinical trials on reperfusion injury inhibitory strategies in patients with AMI.

PATHOPHYSIOLOGY OF ACUTE MYOCARDIAL INFARCTION: PLAQUE STABILITY

The distribution of macrophages and smooth muscle cells within atherosclerotic plaques is highly variable, which is clinically relevant because these cell types have opposite effects on the stability of atherosclerotic plaques.[1] Several risk factors for atherosclerosis, including hemodynamic factors, may be implicated in determining the cellular composition of plaques. The study described in Chapter 2 was the first study that showed marked topographic variation in cellular composition within atherosclerotic plaques related to the direction of the blood stream. It was shown that there were significant differences in cell composition between upstream and downstream parts of plaques suggesting a role for arterial flow in the distribution of different cell types. The downstream areas of plaques contain significantly more smooth muscle cells, which could provide the background for slowly progressive growth at distal ends of plaques. In contrast macrophages are the dominant cell types in the upstream/high shear stress areas, inducing plaque degrading. Plaque instability leading to plaque rupture is currently considered to be an imbalance between reparative activities (smooth muscle cell growth and collagen synthesis) and degrading activities induced by macrophages.[1-3] Subsequent studies confirmed that plaque instability and rupture occurred predominately in the upstream stress areas[4,5] and that this is, at least partly, related to shear stress patterns.[5,6] Obviously, we will not be able to change shear stress patterns, but it may be possible to influence macrophage recruitment and plaque stability with the use of fibrates and statins. Statins have been shown to improve clinical outcome in patients with coronary artery disease partly due to plaque stabilization, thereby reducing plaque vulnerability.[7,8] These effects may be exerted independent of the effects on serum cholesterol.[8,9] Novel agents, such as agents with mast-cell, integrin and chemokine blockade and interleukin-10, are now being investigated in experimental models with their respect to their macrophage and plaque stabilizing properties and need to be awaited.

In conclusion, the large amount of macrophages in the upstream parts of plaques indicate a relationship between high flow/high shear stress and plaque content and plaque stability. This may result in an upstream site of plaque rupture, leading to acute coronary syndromes including acute myocardial infarction.

DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION: THE ELECTROCARDIOGRAM

More than 100 years after Einthoven's first publication on the electrocardiogram,[10] the interpretation of the electrocardiogram, in combination with the clinical presentation, is crucial for diagnosis of AMI. It is a non-invasive, cheap and widely available diagnostic tool. Several electrocardiographic criteria to diagnose the site of occlusion in the coronary artery have been published and it has been claimed that, by careful interpretation of the electrocardiogram based on electrical vector theory, it is possible to predict the culprit coronary segment.[11,12] However these criteria were mainly based on (electrical vector) theories or non-blinded studies and there was a need to evaluate these criteria in clinical practice in a blinded setting, which was described in Chapter 3. The analysis of the electrocardiogram to predict the culprit coronary segment was correct in only 39% (60/153). Consequently, in the total study population and in all subgroups the sensitivity and specificity values to detect a large area at risk due to a proximal site of coronary occlusion were low. Prediction of the culprit segment or the adjacent segment resulted in 75% correctness. Thus, in practice the electrocardiogram is appropriate for detection of an AMI, but it appeared to have low accuracy for exact prediction of the infarct related coronary segment or a large area at risk, even when interpreted by an expert. Large areas at risk were accompanied by electrocardiograms with limited ST-segment elevation in a considerable number of patients. Given this inaccuracy of the acute electrocardiogram, the electrocardiogram should not be used for selecting a treatment strategy in patients with suspected ST-segment elevation myocardial infarction. The findings of this study underscore the importance of immediate coronary angiography in patients with the typical clinical presentation of AMI and any degree of ST-segment elevation.

In conclusion, the electrocardiogram appeared to be inaccurate, with low sensitivity and specificity to predict the exact site of coronary occlusion. Despite these limitations, interpretation of the electrocardiogram remains the investigation of choice for the diagnosis of the presence of an acute myocardial infarction.

TREATMENT OF ACUTE MYOCARDIAL INFARCTION: NOVEL TREATMENT STRATEGIES IN PRIMARY PCI

The principal therapy in patients with an AMI to limit infarct size is myocardial reperfusion by revascularization with a mechanical (percutaneous coronary intervention) or pharmacological intervention (thrombolysis).[13] Limitation of myocardial infarct size is critical to improve immediate and long-term outcome and to reduce the incidence and prevalence of heart failure.

Primary Percutaneous Coronary Intervention Using the Transradial Approach

In Chapter 4 it was demonstrated that the primary percutaneous coronary intervention using the transradial approach is feasible. It has been proven in prior studies that treatment with a glycoprotein IIb/IIIa receptor blocker improves clinical outcome in patients with an AMI.[14-17] However, the use of glycoprotein IIb/IIIa receptor blockade may induce adverse bleeding complications.[15] Additionally, it was recently shown that when a glycoprotein IIb/IIIa receptor blocker was administered about one hour before primary percutaneous coronary intervention it did not result in improved outcome when compared to administration in the catheterization laboratory.[18] Alternatives, such as bivalirudin, may result in similar beneficial effects, but less adverse bleeding complications.[19] Using the transradial approach, primary percutaneous coronary intervention resulted in few entry-site complications and a high procedural success-rate (96%). More recent (unpublished) data show even higher success rates, that increase with experience. Although the transradial approach will take a few more minutes, the benefits may prevail especially concerning bleeding complications and early mobilization. Despite an aggressive anti-thrombotic treatment regimen with glycoprotein IIb/IIIa receptor blockade there were very few bleeding complications. Other studies have also shown that with the transradial approach in acute coronary syndrome, bleeding complications were less compared to the more routinely used transfemoral approach.[20] Bleeding has been shown to correlate with subsequent major cardiovascular events and patient mortality.[21] In addition, the results in Chapter 4 show that the strategy of early revascularization with stenting and the transradial approach under glycoprotein IIb/IIIa receptor blockade followed by early mobilization and early discharge was feasible. It should be appreciated that our study population consisted of a high risk group for adverse outcome: 31% of patients in the current study was ≥ 70 years, the percentage of anterior myocardial infarction was high (69%) and 28% of patients had angiographic multi-vessel disease. Despite this, clinical adverse events remained low throughout one year follow-up.

In conclusion, the strategy of early revascularization by the transradial approach under glycoprotein IIb/IIIa receptor blockade followed by early discharge was feasible in patients with an acute myocardial infarction. The use of the transradial approach will likely result in fewer bleeding complications, even under aggressive anti-thrombotic regimen, and may therefore become the preferred method for primary percutaneous coronary intervention.

Drug-Eluting Stents in Acute Myocardial Infarction

Drug-eluting stents have been shown to reduce target-vessel revascularization as compared with bare-metal stents in a variety of clinical settings.[22,23] Chapters 5 and 6 contain the results of the PASSION trial, one of the first randomised trials, investigating the use of a drug-eluting stent in patients with AMI. The PASSION trial investigated the efficacy of the paclitaxel-eluting stent (TAXUS®) compared to conventional bare-metal stents in 619 patients with an AMI. The one and two year follow-up showed marked, but non-significant, reduction on the occurrence of major adverse cardiac events as cardiac death, recurrent myocardial infarction, and target lesion revascularization in patients treated with a paclitaxel-eluting stent compared to a conventional bare-metal stent. The risk reduction for the combined endpoint cardiac mortality, recurrent myocardial infarction or target lesion revascularization was approximately 30%, which certainly is clinically relevant. This risk reduction was predominantly caused by limitation of restenosis, thereby leading to a reduction of target lesion revascularization. At two years follow-up the relative risk reduction for target lesion revascularization was slightly higher (40%), but this failed to reach levels of statistical significance likely as a result of a lower than expected rate of target lesion revascularization in the bare-metal stent group (causing a type ß-error). The simultaneously published results of the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON) study, evaluating the efficacy of the sirolimus-eluting stent (Cypher®) in AMI with a similar number of patients, did show a significant benefit.[24] Apart from the employed employ type of drug and stent, there were several distinct differences between these two trials, including: 1) A higher rate of need for revascularization in the bare-metal stent group in the TYPHOON study compared to the PASSION trial, 13.4% versus 7.8%; 2) Differences in the inclusion and exclusion criteria; 3) The performance of control angiography in the TYPHOON study which may have increased the revascularization rate due to the "oculo-stenotic reflex". The performance of control angiography in clinical trials does not only differ from routine clinical practice (the real-world) and induces bias, it also exposes the patients to additional risk from repeat catheterization and revascularisation by percutaneous coronary intervention or coronary artery bypass grafting.

The results of the additional meta-analysis of eight randomised controlled trials in Chapter 7 confirmed these beneficial effects of drug-eluting stents in AMI. The analysis included 2.786 patients with a mean follow-up of 12 to 24 months and showed that the use of drug-eluting stents in AMI significantly limited the occurrence of major adverse cardiac events, both with the paclitaxel- and the sirolimus-eluting stent. Similar to all drug-eluting stent trials the benefit was mainly driven by limiting the need for target lesion revascularization and a trends towards beneficial effects on the occurrence of recurrent myocardial infarction and death.

A statement was released by the Food & Drug Administration panel in November 2006 which cautioned that off-label use of drug-eluting stents (including for AMI) is associated with increased risks of both early and late stent thrombosis. Restenosis is considered a relatively

benign entity resulting in stable coronary syndromes, while stent thrombosis can be a potentially lethal adverse event. Since the event rates late after primary percutaneous coronary intervention for AMI with drug-eluting stents were unknown, longer follow-up after drug-eluting stent implantation seemed warranted, especially after discontinuation of thienopyridines (e.g. clopidogrel [Plavix®]). Our two year results of the PASSION trial in Chapter 6 did not show an increase of late-stent thrombosis 1 year after the discontinuation of clopidogrel. Additionally, the meta-analysis with a follow-up up to 18-24 months in Chapter 7 showed similar reassuring results . Nevertheless, the use of drug-eluting stents in AMI remains debatable, and it may not be mandated in view of the predominantly large size of culprit vessels with a low expected risk of restenosis, yet these trials demonstrate a reduction in procedures for restenosis and favourable trends to lower deaths and recurrent myocardial infarction with drug-eluting stents.

Overall, the beneficial effects of drug-eluting stents also appear to prevail in patients with acute myocardial infarction predominantly by a reduced need for target lesion revascularization compared to bare-metal stent implantation. These beneficial effect were not statistically significant when evaluated in 619 patients in our studies, but were significant when evaluated in a larger study population (meta-analysis). Importantly, the rates of stent thrombosis were not increased after paclitaxel-eluting or sirolimus-eluting stent implantation in primary percutaneous coronary intervention for acute myocardial infarction two years after stent implantation and one year after discontinuation of clopidogrel. These observations warrant the execution of larger trials with longer follow-up to better assess the effectiveness, risks and cost-effectiveness of drug-eluting stents in acute myocardial infarction.

SEQUELAE OF ACUTE MYOCARDIAL INFARCTION: REPERFUSION INJURY

The importance of early reperfusion by thrombolysis or primary percutaneous coronary intervention is not surprising as the primary insult is a decrease in oxygen supply resulting in a decrease of free energy from ATP-hydrolysis beyond a critical level required for maintaining cell processes. However, despite its clear benefit, reperfusion itself has been proposed to cause irreversible myocardial damage, termed "reperfusion injury". The mechanism of reperfusion injury remains incompletely understood and direct evidence for the existence of reperfusion injury stems from animal studies in which pharmacological agents administered just prior to reperfusion limit infarct size.[25-30] Pre-clinical studies, although sometimes equivocal, spurred a large number of clinical trials (~ 39 trials). Chapters 8 and 9 describe the results of two of these randomised clinical trials which evaluated the efficacy of two reperfusion inhibitory agents (ITF-1697 in the Protect Against Reperfusion Injury with ITF-1697 in acute Myocardial Infarction [PARI-MI] and caldaret in the CAldaret [MCC-135] in patients undergoing primary percutaneous coronary intervention for ST-segment Elevation Myocardial Infarction

[CASTEMI] trial). The PARI-MI and the CASTEMI trial used agents that target two different pathways of the reperfusion injury cascade and showed similar disappointing results. Both agents failed to limit infarct size or improve clinical outcome. Although treatment with other agents, especially those agents affecting the inflammatory response to ischaemic and reperfusion injury,[31,32] may theoretically cause adverse events by interfering the physiological healing and scarring process, treatment with ITF-1697 and caldaret appeared to be safe.

The pre-clinical data of both ITF-1697 and caldaret demonstrated beneficial effects in various experimental models. However, the pre-clinical evidence was limited and predominantly based on unpublished data. In view of the disappointing results in the clinical setting of AMI both studies further amplified the need for more careful review of pre-clinical and clinical studies with reperfusion injury inhibitory agents in general. In Chapter 10 this topic was reviewed discussing the encouraging results from animal studies with absence of benefit in clinical studies on reperfusion injury inhibitory strategies. Potential explanations for these discrepant findings are numerous and include: the absence of co-morbid conditions and concomitant medication in the animal models; differences in duration and mode of vessel occlusion; timing of administration of the reperfusion injury inhibitory drug; and differences in study endpoints. Future studies into novel drugs that have shown promise in the experimental setting should take these factors into account. Considering the numerous prior trials evaluating reperfusion inhibitory agents there is low likelihood of success in patients with AMI. To prevent inappropriate clinical trials with new agents, these trials should be initiated only after the therapy proves to be reproducibly effective and safe in different animal models, ideally performed in a randomised, blinded and multicenter approach, analogous to clinical trials. Only then clinical testing should be started, initially focusing on predefined subgroups for proof of concept, before conducting a large scale clinical trial.

In conclusion, the evidence presented suggests that future studies pertaining to limitation of ischaemia-reperfusion injury in patients with acute myocardial infarction have a low likelihood of success. There are numerous factors, in both the experimental and clinical studies, responsible for these disappointing results in patients with acute myocardial infarction, and future investigations into this field should take these factors into account.

RECOMMENDATIONS FOR STATE OF THE ART CLINICAL PRACTICE

The results from this thesis warrant the following protocol for treatment of patients with an AMI: (1) An onsite electrocardiogram should be made by paramedics from all patients with suspected AMI. This electrocardiogram may be transferred to the nearest interventional center and judged. (2) If, the electrocardiogram shows ST-segment elevation indicating an AMI, irrespective of the amount of ST-segment deviation, the patient receives a loading dose of aspirin and is transferred to the interventional center. (3) On arrival at the center the diagnosis

is verified at the catheterization laboratory, a loading dose of thienopyridines is administered and an emergency coronary angiography is performed. Although the use of a glycoprotein IIb/IIIa receptor blocker is recommended as an adjunct to primary percutaneous coronary intervention, in our center it is only added to the treatment regime in case of no-reflow or a complicated percutaneous coronary intervention, this is due to high costs and potential bleeding complications. At our center all patients undergo the procedure with the transradial approach. (4) Subsequently, a primary percutaneous coronary intervention with stenting is performed when indicated. A drug-eluting stent is merely used in patients with a high likelihood to develop restenosis (e.g. diabetes mellitus, small diameter of the culprit vessel). Currently, there are no specific drugs administered to reduce reperfusion injury. (5) Once the patient is clinically stabilized, pharmacological treatment with daily asprin, thienopyridines, beta-blockers, statins, and, if indicated, ACE-inhibitors is initiated. Finally, patients are discharged three to four days after the event, provided that hospital stay remained uncomplicated.

FUTURE DIRECTIONS IN TREATMENT OF ACUTE MYOCARDIAL INFARCTION

This thesis describes strategies to further improve treatment of patients with an AMI. Future treatments to further improve clinical outcome in patients with AMI should be aimed at reduction of the number of patients not receiving reperfusion therapy and limitation of infarct size by faster diagnosis and treatment, limitation of restenosis, limitation of stent thrombosis and regeneration of infarcted myocardium in patients with severe myocardial damage.

"Time is Muscle": Faster Diagnosis and Treatment

The earlier an AMI is diagnosed and the sooner a patient is treated the better the outcome will be. Patient awareness and education in order to recognize ischaemic complaints earlier may prevent patient delay. Earlier diagnosis can be achieved by immediate pre-hospital electrocardiography, which might then be transmitted to an interventional center for verification or be interpreted by computer algorhythms. As discussed in chapter 3, patients with an electrocardiogram showing any ST-segment elevation should be transferred as soon as possible to the nearest interventional center for coronary angiography and, if indicated, primary percutaneous coronary intervention. In case percutaneous coronary intervention is unavailable immediate treatment with thrombolysis should be initiated, if possible administered already prior to arrival at the hospital. In addition, anti-thrombotic treatment with aspirin, thienopyridines and (low-molecular weight) heparin should be initiated as soon as possible. Finally, future strategies should also be aimed at improving pre- and in-hospital patient logistics, in order to reduce the time from onset of symptoms to reperfusion.

Improvements in Stent Design

Apart from the use of drug-eluting stent, limitation of restenosis and reduction of stent thrombosis may also be achieved by improved stent design, including the use of biodegradable stent material. Animal studies and numerous randomised trials have indicated that stent design does indeed have a profound effect on the tissue response, thereby exerting a significant influence on restenosis and stent thrombosis.[33-35] Currently, stents have widely disparate strut thickness, shapes and surfaces, are made of different material, with a variant amount of strut-to-strut intersections, coatings and polymers (the latter in case of drug-eluting stents).[36] There is a fragile balance between the strut thickness of the stent and its short and long-term outcome. Although direct stent performance may be improved by increasing strut thickness which consecutively increases radio-visibility; radial force and arterial wall support, conversely, excessive strut thickness may induce vascular injury and trigger intimal hyperplasia, resulting in an increase of restenosis compared to thinner struts.[34] In an effort to further reduce strut thickness while maintaining adequate radio-visibility and radial strength, novel metallic materials such as cobalt-chromium alloy are being used for the production of stents.[35]

On the other hand, the ideal drug-eluting stent may need to have a large surface area of contact with the vascular wall, minimal gaps, robust radial support and symmetrical expansion to ensure uniform drug elution. At the same time, it would need to be slim and flexible to enable successful deployment in complex lesions. Moreover, there is a major concern for potential long-term adverse effects caused by the carrier of the drug. Synthetic polymers are the most widely used carriers for anti-mitotic drugs which may induce an enhanced inflammatory reaction and possibly a prothrombotic response.[37] The latter could be avoided by the use biomimetic and biodegradable polymers which are currently developed.

In contrast to drug-eluting stents, that interfere with the natural healing response by preventing the formation of a functional endothelial lining over the stent, early establishment of a functional endothelial layer after stent implantation may prevent of neointimal proliferation and thrombus formation.[38,39] In two pilot studies it was investigated whether stents covered with monoclonal anti-human CD34 antibodies or integrin-binding cyclic Arg-Gly-Asp peptide could limit coronary neointima formation and accelerate endothelialization by attracting endothelial progenitor cells.[40,41] Both bioengineered stents showed safety and promise in initial clinical studies, but still need to be evaluated in larger study populations.

Theoretically vessel scaffolding may be necessary only for a certain, limited time.[36,42] Bioabsorbable or biodegradable stents are made of material that will be totally absorbed within a few weeks or months. Consequently no stent or stent material will be left behind, thereby possibly reducing chronic inflammation aggravating restenosis. The need for long-term use of clopidogrel post-stenting will may also no longer be necessary, since the occurrence of stent thrombosis is not very likely, provided that the endothelium is functional. With the use of bioabsorbable stents it will be less problematic to re-intervene the treated lesion in case of restenosis with either percutaneous coronary intervention or coronary-artery bypass grafting.

Furthermore, bioabsorbable stents will allow the vessel to perform physiological positive outward remodelling and may be associated with a normal endothelial function. Similar to elective percutaneous intervention, after AMI, healing of the endothelium is mandatory. Therefore improvements in stent design should be aimed at allowing normalisation of endothelial function. Nevertheless, there remain some challenges for the design and application of bioabsorbable stents, such as the time and rate of degradation (preferably 12-24 months),[36] biocompatibility, radio-opacity, and remaining polymer and elution of possible drugs from bioabsorbable stents. The first clinical trials with bioabsorbable stents in patients with stable coronary syndromes have already been performed in which they showed to be safe with an acceptable rate of restenosis and no occurrence of stent thrombosis.[42] The employment of bioabsorbable stents in patients with AMI may have similar beneficial effects.

Regeneration of Infarcted Myocardium

It has been suggested that tissue regeneration with stem cell or gene therapy may restore left ventricular function after AMI.[43] This may be of particularly interest to patients with extensive myocardial damage due to failure or inability of early reperfusion therapy. As left ventricular function is one of the most important parameters for survival and morbidity, restoration of left ventricular function remains one of the major targets in treatment of AMI. However, there is a need for intensive fundamental research in this field of tissue regeneration as there remain major issues to be resolved. First, there is a need for competent stem cells that are capable of self renewal and differentiation that are easily available and engraftable without inducing ventricular damage. Secondly, it remains complex to deliver these cells at the infarcted tissue in a proper fashion (direct ventricular injection or (intracoronary) catheter based injection). The injection of cells may also induce hazard such as myocardial necrosis with intra-coronary injection of large cells (e.g. mesenchymal stromal cells or umbilical cord derived somatic stem cells) or large numbers of cells[44] and it may induce increased restenosis or atherosclerotic progression.[45] Thirdly, the stem cells itself can cause an unexpected (local) adverse events, such as inflammation, fibrosis or calcification. Finally, injection of cells may cause inadvertent transmission of infectious agents (e.g. prions).

Treatment aimed at regeneration with tissue regeneration with stem cell therapy would potentially meet a unmet need, especially with the high mortality in the high risk AMI groups. The experimental data is still incomplete, but promising. Some clinical studies have recently been initiated and initial results, although mixed, overall appeared promising.[46,47] Analogous to the studies evaluating reperfusion injury inhibitory strategies the experimental data were far more promising. Future experimental trials, also in the field of tissue regeneration, should be performed in a multicenter, blinded and randomised manner and in models resembling the clinical setting of AMI more closely.

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NEDERLANDSE SAMENVATTING

Hart- en vaatziekten zijn nog altijd de meest voorkomende ziekte en de belangrijkste oorzaak van sterfte Westerse wereld. Het acute hartinfarct (myocardinfarct) is verantwoordelijk voor het grootste deel van de plotse doden. De behandeling van het hartinfarct is gericht op beperking van de infarctgrootte, die de prognose voor een groot deel bepaalt. Dit proefschrift beschrijft verschillende aspecten van het ontstaansmechanisme, de diagnose en de behandeling van het acute hartinfarct (myocardinfarct). Meer specifiek was het doel om:

1) meer inzicht te krijgen in het ontstaansmechanisme (de *pathofysiologie)* van atherosclerotische plaque-instabiliteit op celniveau.
2) de precisie te evalueren van het electrocardiogram ter *diagnose* van het myocardinfarct.
3) de spoed- of 'primaire' percutane coronaire interventie (de huidige standaard-*behandeling* van het hartinfarct) te optimaliseren.
4) de eventuele nadelige *gevolgen* van deze behandeling, zoals de paradoxale 'reperfusieschade', te beperken.

PATHOFYSIOLOGIE VAN HET ACUTE HARTINFARCT

Atherosclerose ("aderverkalking") is een ziekteproces in de wand van een slagader (arterie), die leidt tot hart- en vaatziekten. Wanneer een atherosclerotische plaque instabiel wordt met lokale stolselvorming en/of een ruptuur (openbarsten van een plaque), kan een plotse afsluiting (occlusie) van een slagader ontstaan. Op het moment dat een plotse afsluiting ontstaat in een van de kransslagaders (coronaire arteriën), die het hart voorzien van bloed, krijgt een deel van het hart geen bloed en daardoor ook geen zuurstof. Dit deel van het hartspierweefsel (myocard) wordt dan 'ischemisch' en zal niet meer naar behoren functioneren. Blijft deze ischemische situatie langer dan een half uur bestaan dan zal het hartspierweefsel uiteindelijk afsterven (infarceren).

In hoofdstuk 2 is op celniveau gekeken naar de verdeling van gladde spiercellen (smooth muscle cells (SMC)) en macrofagen (afweercellen die lichaamsvreemde stoffen en beschadigde of gedode micro-organismen (o.a. bacteriën en virussen) en hun afvalstoffen in zich opnemen en onschadelijk maken) in 33 atherosclerotische plaques (aantastingen). Hieruit blijkt dat de groei en instabiliteit van een atherosclerotische plaque mogelijk afhankelijk is van de stroomrichting en de zogenaamde 'shear stress' op de plaque. Shear stress is de afschuifspanning van de bloedstroom op de vaatwand. Stabiele en langzame plaquegroei onder invloed van gladde spiercellen vindt vooral plaats in het stroomafwaartse deel van een plaque, waar een lage shear stress heerst. Instabiliteit van een plaque, met een verhoogde kans op erosie en ruptuur tot gevolg, is onder andere geassocieerd met de aanwezigheid van macrofagen. Deze macrofagen zijn voornamelijk te vinden in het stroomopwaartse deel van een plaque. Hieruit blijkt dat de er een relatie bestaat tussen plaque-instabiliteit, de stroomrichting van het bloed en shear stress. Dit verband werd later bevestigd door onderzoeken waarin men

observeerde dat plaque-erosie en -ruptuur inderdaad vooral in de stroomopwaartse delen van de plaque plaatsvinden. Op grond deze en andere observaties is men thans naarstig op zoek naar geneesmiddelen met een plaquestabiliserende werking.

De grotere dichtheid van macrofagen in het stroomopwaartse deel van een atherosclerotische plaque wijst op een relatie tussen de stroomrichting van het bloed en shear stress met plaque-instabiliteit, die op zijn beurt kan leiden tot een stroomopwaarts gelokaliseerde plaqueruptuur, met een acuut coronair syndroom zoals een acuut hartinfarct tot gevolg.

DIAGNOSTIEK VAN HET ACUTE HARTINFARCT: HET ELECTROCARDIOGRAM

De typische presentatie van een acuut hartinfarct is een patiënt met pijn of druk op de borst, al dan niet met uitstraling naar de armen en/of kaken, met of zonder vegetatieve verschijnselen (misselijkheid, braken en overmatig zweten) gedurende tenminste 20 minuten. De diagnose wordt gesteld met behulp van het electrocardiogram (ECG) in combinatie met deze klachten. Meer dan 100 jaar na de introductie van het ECG door Einthoven is het ECG een onmisbaar diagnosticum voor een grote verscheidenheid aan cardiale pathologie, waaronder het acute hartinfarct. Het ECG (een registratie van de elektrische activiteit van de hartspier) is vrijwel overal beschikbaar, niet invasief en goedkoop. Het ECG is niet alleen van belang voor het stellen van de diagnose zelf, maar de mate en de lokatie van de ST-segmentsafwijkingen (ST-elevaties en –depressies) op het ECG weerspiegelen ook de grootte en de lokatie van het bedreigde gebied, zodat kan worden afgeleid in welk segment van welke kransslagader zich de afsluiting bevindt. De criteria hiervoor zijn gebaseerd op de zogenaamde elektrische vector theorie en het werd tijd voor een gevalideerde en geblindeerde toetsing van deze criteria (hoofdstuk 3). ECG's (n = 153) werden door een expert in de electrocardiografie geïnterpreteerd, terwijl hij geblindeerd was voor de uiteindelijke bij coronairangiografie (röntgenfilm met contrast van de kransslagaders) vastgestelde afsluiting in de kransslagader. Het staat buiten kijf dat het ECG onmisbaar blijft om de diagnose acuut hartinfarct te stellen, doch het blijkt niet erg nauwkeurig voor de bepaling van de precieze lokatie van de afsluiting in de kransslagader. Slechts in 39% (60 van de 153 ECG's) bleek de door interpretatie van het ECG voorspelde lokatie van de afsluiting in de kransslagader overeen te komen met de daadwerkelijk aangetoonde lokatie. De sensitiviteit (de hoeveelheid zieken die ook daadwerkelijk als ziek worden aangemerkt door de test) en de specificiteit (de hoeveelheid door de test aangewezen niet-zieken die daadwerkelijk niet ziek zijn) van het ECG om de precieze lokalisatie van de coronaire occlusie bij grote hartinfarcten aan te tonen waren dientengevolge laag, respectievelijk 47% en 57%. Het bleek dat een groot aantal patiënten met een groot bedreigd gebied maar weinig ST-segmentsdeviatie op het ECG toonden. Ons inziens dient men dus niet te veel te varen op wat het ECG aangeeft met betrekking tot de lokatie van de afsluiting in de kransslagader en de grootte van het bedreigde gebied. Patiënten met een acuut ST-segment elevatie myocard-

infarct (STEMI) dienen dan ook altijd met spoed coronairangiografie en zo nodig een spoed dotterprocedure ('primaire' percutane coronaire interventie (PCI)) te ondergaan, ongeacht de mate van en elektrische vector van de ST-elevaties.

Concluderend, in patiënten met een acuut hartinfarct blijkt het ECG geen betrouwbaar diagnosticum te zijn voor de bepaling van de grootte van het bedreigde gebied en/of exacte lokalisatie van het de afsluiting. Ondanks deze beperking blijft het ECG wel hét diagnosticum bij uitstek voor de diagnose van het hartinfarct.

BEHANDELING VAN HET ACUTE HARTINFARCT: NIEUWE BEHANDELINGSSTRATEGIEËN TER VERBETERING VAN DE PRIMAIRE PERCUTANE CORONAIRE INTERVENTIE

De optimale therapie voor een acuut ST-segment elevatie myocardinfarct (STEMI) is het zo snel mogelijk revasculariseren ('heropenen') van het aangedane bloedvat, hetzij met een spoed dotterprocedure ('primaire' percutane coronaire interventie (PCI)), hetzij farmacologisch met trombolyse (het medicamenteus oplossen van het afsluitende stolsel). Zoals eerder gesteld, beperking van de infarctgrootte is het belangrijkste doel om de ziekte-vrije overleving en het ontstaan van hartfalen op korte en lange termijn te verbeteren. Thans wordt primaire PCI met stentimplantatie gezien als de optimale behandeling van patiënten met een STEMI en effectiever dan trombolyse of ballondilatatie zonder stentplaatsing. In de hoofdstukken 4 tot en met 7 is onderzocht of nieuwe strategieën gericht op het verminderen van complicaties van PCI en restenose (het opnieuw vernauwd raken van een kransslagader ter plaatse van met PCI behandelde stenose) de resultaten van primaire PCI met stenting verder kunnen verbeteren.

Primaire Percutane Coronaire Interventie met de Transradiale Benadering

Rondom een primaire PCI kunnen medicijnen gegeven worden die tot doel hebben de uiteindelijke hartinfarctgrootte te beperken en tromobotische complicaties (bloedpropjes in de bloedbaan) ten gevolge van de PCI of stentplaatsing zelf te voorkomen. Momenteel is het gebruik van heparine en bloedplaatjesaggregatietremmers, zoals carbasalaatcalcium of acetylsalicylzuur (aspirine) en thienopyridines (clopidogrel en ticlopidine), standaardtherapie voor patiënten met een acuut coronair syndroom, waaronder ook het STEMI. De afgelopen jaren heeft men ook het effect geëvalueerd van de mogelijk meer potente intraveneuze bloedplaatjesaggregatietremmers glycoproteïne IIb/IIIa (GPIIb/IIIa) receptorblokkers (tirofiban, abciximab, eptifibatide). GPIIb/IIIa receptorblokkers verbeteren de microvasculaire doorbloeding van het hartspierweefsel en verminderen de distale embolisatie (het verder meevoeren van bloedpropjes in de bloedbaan en het verderop afsluiten van een slagader) en de trombusmassa, waardoor de uiteindelijke schade aan het hart beperkt wordt. Bij een PCI wordt de stenose (vernauwing) in de kransslagader mechanisch met ballon en stent weg-

geperst en opgeheven. Hierbij kan plaque- inhoud en trombotisch weefsel loskomen en raakt het endotheel (binnenste laag van de vaatwand) beschadigd. Hierdoor ontstaat een milieu dat stolselvorming bevordert. GPIIb/IIIa receptorblokkers gaan dit juist tegen.

Echter, het gebruik van GPIIb/IIIa receptorblokkers in combinatie met orale bloedplaatjesaggregatietremmers en heparine gaat ook gepaard met een verhoogd bloedingsrisico, voornamelijk ter plaatse van de insteekopening in de bloedbaan van de catheter (12% in the ADMIRAL-trial), met een verhoogde morbiditeit en een verlengd ziekenhuisverblijf als gevolg. Door gebruik te maken van de transradiale benadering of "transradial approach" (TRA), waarbij men de kransslagaders via de polsslagader (arteria radialis) benadert in plaats van via de liesslagader, kunnen belangrijke bloedingscomplicaties worden vermeden. In hoofdstuk 4 is geëvalueerd of het mogelijk was om patiënten met een acuut hartinfarct na een korte ziekenhuisopname (3-4 dagen) veilig naar huis te ontslaan na behandeling met primaire PCI en de transradiale benadering in combinatie met GPIIb/IIIa receptorblokkers. Honderd patiënten werden op deze wijze behandeld en ontslagen. Deze strategie bleek veilig en goed toepasbaar in de klinische praktijk, hoewel grotere en eventueel gerandomiseerde onderzoeken zouden moeten worden uitgevoerd om te bestuderen of deze strategie ook daadwerkelijk superieur is aan andere strategieën. Primaire PCI via de transradiale benadering resulteerde in een hoog succespercentage (96%) en weinig complicaties. De behandelingsstrategie van primaire PCI via de TRA onder behandeling met GPIIb/IIIa receptorblokkers zorgde ervoor dat patiënten snel konden mobiliseren en reeds 3-4 dagen na het acute hartinfarct veilig uit het ziekenhuis konden worden ontslagen. Het optreden van ernstige klinische gebeurtenissen bleef gedurende het jaar na het hartinfarct laag in de studiepopulatie. Thans is de transradiale procedure de standaard in het Onze Lieve Vrouwe Gasthuis, met een inmiddels nog hoger succespercentage. Ondanks het feit dat de TRA een paar minuten extra tijd kost, lijken de voordelen van de TRA hier ruimschoots tegen op te wegen. Vooral door de vermindering van bloedingscomplicaties bij patiënten die met agressieve en intensieve antitrombotische medicatie worden behandeld.

Samenvattend kan gesteld worden dat de gecombineerde strategie van spoed PCI, de TRA, het gebruik van GPIIb/IIIa receptorblokkers en vroeg ontslag mogelijk is bij patiënten met een acuut hartinfarct. Zelfs bij patiënten die behandeld worden met agressieve antitrombotische medicatie, leidt het gebruik van de TRA mogelijk tot minder bloedingscomplicaties en zou derhalve te prefereren zijn boven de meer conventionele transfemorale methode.

Drug-Eluting Stents bij Primaire PCI voor het Acute Hartinfarct

Een revolutie in de interventiecardiologie is het gebruik van een nieuw soort stent, de 'drug-eluting stent' (DES). Bij patiënten met een acuut hartinfarct die behandeld zijn middels primaire PCI met plaatsing van een conventionele ofwel 'bare-metal stent' (BMS) kan restenose ontstaan. Er is zelfs melding gemaakt van een restenosepercentage van 20%. Een zogenaamde DES geeft een geneesmiddel af dat het opnieuw dichtgroeien van de lesie

(restenose) ter plekke tegengaat. Het opnieuw dichtgroeien wordt voornamelijk veroorzaakt door een ontstekingsreactie die het gevolg is van de schade die aan het bloedvat wordt toegebracht bij het aanbrengen van de stent. Bij die ontstekingsreactie worden nieuwe cellen aangevoerd die de stent inkapselen. De geneesmiddelen op een drug-eluting stent remmen deze ontstekingsreactie en de groei van weefsel in en rondom de stent. Het gebruik van deze DES in de behandeling van obstructief coronairlijden zorgt voor een dramatische afname van het optreden van restenose en leidt dientengevolge tot een lagere incidentie van angineuze symptomen (pijn op de borst), nieuwe hartinfarcten, sterfte en de noodzaak voor het opnieuw behandelen van dezelfde kransslagaders middels PCI of een open hartoperatie (CABG: coronary artery bypass grafting). Momenteel zijn er meerdere soorten DES op de markt van verschillende materialen die verschillende soorten medicatie afgeven. De eerste twee soorten DES die op de markt verschenen waren de sirolimus-eluting stent en de paclitaxel-eluting stent (PES)(TAXUS®). Van beide is de effectiviteit aangetoond in het tegengaan van restenose in patiënten met stabiel obstructief coronairlijden. Deze DES waren echter nooit eerder onderzocht bij patiënten met een acuut hartinfarct die primaire PCI ondergingen. Aangezien de atherosclerotische plaque bij stabiel coronairlijden belangrijke verschillen vertoont vergeleken met de instabiele en trombotische plaque bij instabiel coronairlijden, zoals het acute hartinfarct, is het de vraag of het gebruik van DES ook zinvol is in de behandeling van patiënten met een acuut hartinfarct.

In hoofdstuk 5 worden de resultaten beschreven van de PASSION trial (PAclitaxel-eluting Stent versus conventional Stent in myocardial Infarction with ST-Segment ElevatION), het eerste gerandomiseerde en geblindeerde onderzoek naar de effectiviteit van paclitaxel-eluting stents (PES) in patiënten (n=619) met een acuut hartinfarct. De follow-up na 1 en 2 jaar (hoofdstuk 6) toonde aan dat het gebruik van PES bij patiënten met een acuut hartinfarct niet leidde tot significant minder nieuwe hartinfarcten, doden of nieuwe revasculariserende ingrepen van de behandelde kransslagader als uiting van minder restenose. Wel werd er een trend gezien tussen PES en BMS in deze setting (11.1% versus 15.4%), met een relatieve risicoreductie, ook twee jaar na het initiële hartinfarct, van 30-40%. Deze relatieve risicoreductie werd voornamelijk veroorzaakt door een trend in minder noodzaak voor nieuwe therapeutische interventies ten gevolge van restenose (6.0% versus 9.9%). Dat deze relatieve risicoreductie niet heeft geleid tot een statistisch significant verschil tussen PES en BMS is deels veroorzaakt doordat de studiepopulatie mogelijk te klein was (zogenaamde 'bèta-fout') en deels het gevolg van een lager dan verwacht restenosepercentage in de BMS groep. Wellicht kan dit lage percentage verklaard worden doordat de gebruikte BMS (Express2® en Liberté® stent) zelf een moderne, hightech, doorgeëvolueerde stent is met verbeterde biocompatibiliteit, flexibiliteit en dunne 'struts'. Tegelijkertijd met de publicatie van de PASSION trial werd de Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON) studie gepubliceerd. De TYPHOON studie onderzocht het gebruik van een andere DES, de sirolimus-eluting stent, bij een zelfde hoeveelheid patiënten (n=712)

met een acuut hartinfarct. Dit onderzoek toonde wél significant betere resultaten met het gebruik van sirolimus-eluting stents vergeleken met een BMS. Afgezien van het feit dat de twee onderzoeken (PASSION en TYPHOON) het effect van twee verschillende soorten DES evalueerden, zijn deze studies zeker niet direct vergelijkbaar door een verschil in opzet, in- en exclusiecriteria en definities van eindpunten.

Een belangrijke onderzoeksmethode naar effectiviteit van een behandeling is het bekijken en analyseren van meerdere onderzoeken bij elkaar: Dit noemt men een meta-analyse. De totale studiepopulatie is dus groter, zodat de kans op vals-negatieve of vals-postieve verschillen kleiner wordt (en de 'bèta-fout' voorkomen kan worden). In dit proefschrift is een meta-analyse opgenomen van onderzoeken naar het gebruik van DES bij acute hartinfarcten (hoofdstuk 7). Acht gerandomiseerde onderzoeken zijn geïncludeerd in deze analyse, met in totaal 2.786 patiënten en een klinische follow-up van 18 tot 24 maanden. Het aantal doden was niet verschillend tussen DES of BMS (4.1% versus 5.1%), maar wel verschillend ten aanzien van de noodzaak voor nieuwe interventies ten gevolge van restenose (5.1% versus 13.1%). De analyse ondersteunde de gevonden voordelen van het gebruik van DES bij patiënten met een acuut hartinfarct, zowel met PES als sirolimus-eluting stents.

Desalniettemin is er veel discussie over het gebruik van DES, niet alleen bij patiënten met een acuut hartinfarct, maar bij alle patiënten met obstructief kransslagaderziekte (coronairlijden). De aanleiding is het optreden van (late) stenttrombose. Stenttrombose is het plots afsluiten van een stent, doorgaans door een stolsel (trombus). Doordat het geneesmiddel dat afgegeven wordt door DES de groei van weefsel binnen de stent tegengaat, gaat het ook de noodzakelijke endothelialisatie tegen. Het endotheel, de binnenste laag van de vaatwand, moet het kale metaal van de stent bedekken, omdat kaal metaal in een bloedvat kan leiden tot trombusvorming met alle gevolgen van dien, waaronder acute hartinfarcten en zelfs dood. Eén van de belangrijkste medicijnen die worden gebruikt om stenttrombose tegen te gaan, ook na plaatsing van een BMS, zijn de thienopyridines, met name clopidogrel (Plavix®). Na een acuut hartinfarct worden patiënten 6 tot 12 maanden behandeld met clopidogrel. Er is gesuggereerd dat voornamelijk na het staken van clopidogrel een verhoogde kans (ongeveer 0.6% per jaar) bestaat op het optreden van stenttrombose. Hoe vaak stenttrombose voorkomt na het staken van clopidogrel bij patiënten na een acuut hartinfarct was niet bekend, daarom voerden wij een langtermijnsfollow-up van 2 jaar uit van de PASSION trial. Zowel de follow-up van de PASSION trial als de resultaten van onze meta-analyse lieten zien dat het optreden van stenttrombose bij deze patiënten inderdaad optreedt. In de PASSION studie was dit 2.1% na DES versus 1.4% na BMS implantatie en dit was 1.7% versus 2.2% in de meta-analyse. Een significante toename van stenttrombose met het gebruik van DES werd dus niet aangetoond. Men moet echter wel in ogenschouw nemen dat het voordeel van het gebruik van DES (het verminderen van in-stent restenose), misschien niet opweegt tegen de potentieel schadelijke en zelfs dodelijke complicatie van stenttrombose. Studies hiernaar met een langere follow-up en grotere onderzoekspopulaties zijn dan ook noodzakelijk.

Concluderend kan gesteld worden dat het gebruik van DES in patiënten met een acuut hartinfarct wel enig voordeel heeft, maar het blijft discutabel of het gebruik hiervan noodzakelijk is in alle patiënten met een acuut hartinfarct.

GEVOLGEN VAN HET ACUTE HARTINFARCT: REPERFUSIESCHADE

Zoals reeds genoemd is de behandeling van het hartinfarct gericht op beperking van de infarctgrootte, omdat de prognose met name hiervan afhankelijk is. De therapeutisch of spontane rekanalisatie van het afgesloten vat en de gewenste reperfusie van het myocard die hierdoor optreedt, kan ook nadelige effecten hebben op het hartspierweefsel. Dit fenomeen noemt men 'reperfusieschade'. Het precieze mechanisme van deze reperfusieschade is niet volledig bekend en het concept komt voort uit dierexperimenten, waarin farmacologische agentia werden toegediend vlak voor de reperfusie met als doel beperking van de infarctgrootte. Na gunstige observaties in vele pre-klinische onderzoeken is een groot aantal (± 39) klinische studies gestart, gericht op de behandeling/preventie van reperfusieschade. Hoofdstukken 8 en 9 beschrijven de resultaten van twee gerandomiseerde onderzoeken met reperfusieschade-remmende agentia (ITF-1697 in de "Protect Against Reperfusion Injury with ITF-1697 in acute Myocardial Infarction [PARI-MI]" en caldaret in de "CAldaret [MCC-135] in patients undergoing primary percutaneous coronary intervention for ST-segment Elevation Myocardial Infarction [CASTEMI]"). De PARI-MI (n=402) en de CASTEMI (n=387), waarin verschillende stoffen werden gebruikt, gericht tegen verschillende factoren die bijdragen tot reperfusieschade, toonden beide teleurstellende resultaten. Beide agentia hadden geen (positief noch een negatief) effect op de uiteindelijke infarctgrootte of op het klinische beloop.

De pre-klinische data met betrekking tot zowel ITF-1697 als caldaret toonden veelbelovende resultaten in meerdere, in opzet verschillende diermodellen. Niet alleen door deze twee onderzoeken (PARI-MI en CASTEMI), maar ook door alle voorgaande onderzoeken naar reperfusieschade-remmende medicatie met eenzelfde teleurstellend resultaat, leek het noodzaak om de pre-klinische en klinische onderzoeken die tot nu toe verricht werden onder de loep te nemen. Het laatste hoofdstuk van het proefschrift (hoofdstuk 10) is een overzichtsartikel over alle tot nu toe gedane pogingen reperfusieschade te behandelen in patiënten met een acuut hartinfarct. Het blijkt dat er vele mogelijke verklaringen zijn voor de discrepantie tussen de pre-klinische en klinische resultaten, zoals de afwezigheid van comorbiditeit (o.a. diabetes mellitus, hypertensie, etc), aanvullende medicatie in de diermodellen, grote verschillen in de duur en wijze van vaatocclusie en verschil in onderzoekseindpunten. Toekomstige onderzoeken naar potentieel reperfusieschade-remmende agentia zouden deze en andere factoren meer in ogenschouw moeten nemen. Gezien de teleurstellende resultaten van voorgaande onderzoeken naar reperfusieschade-remmende agentia bij patiënten met een acuut hartinfarct, lijkt de kans op succes van dergelijke interventies klein. Om inadequate

en onvoldoende onderbouwde klinische onderzoeken in de toekomst te voorkomen zouden studies met nieuwe agentia alleen ondernomen mogen worden wanneer de therapie effectief is gebleken in meerdere en verschillende soorten diermodellen. Idealiter zouden deze studies uitgevoerd moeten worden in een geblindeerde, gerandomiseerde, multicenter setting, wat over het algemeen ongewoon is, analoog aan de klinische onderzoeken. Alleen dan zouden klinische onderzoeken opgezet kunnen worden, welke zich initieel zouden moeten richten op specifieke subgroepen ter bevestiging van de werking in patiënten met een acuut hartinfarct.

De resultaten van voorgaande onderzoeken naar reperfusieschade-remmende agentia bij patiënten met een acuut hartinfarct zijn consistent teleurstellend, waardoor de kans op succes voor nieuwe agentia klein lijkt. Er zijn vele verklaringen voor de discrepantie tussen de pre-klinische en klinische studies die in toekomstige onderzoeken in ogenschouw genomen moeten worden.

CONCLUSIE EN AANBEVELINGEN VOOR 'STATE-OF-THE-ART' KLINISCH HANDELEN

Dit proefschrift biedt een overzicht van de pathofysiologie, diagnostiek, behandeling en gevolgen van het acute hartinfarct. Op basis van onder andere de resultaten uit dit proefschrift is er een protocol voor te stellen voor de optimale behandeling van patiënten met een acuut hartinfarct: (1) Bij patiënten met een mogelijk acuut coronair syndroom (waaronder het acute hartinfarct) zou direct en ter plekke (dus ook thuis en op straat) een ECG gemaakt moeten worden door paramedici. Het ECG zou vervolgens per fax of e-mail ter beoordeling doorgestuurd, moeten worden naar het dichtstbijzijnde cardiologisch interventiecentrum. (2) Indien het ECG ST-segment elevaties toont passend bij een acuut hartinfarct zou de patiënt, ongeacht de hoeveelheid en lokalisatie van de ST-segmentselevaties, een oplaaddosis bloedplaatjesaggregatieremmers toegediend moeten krijgen en zo snel mogelijk naar het interventiecentrum getransporteerd moeten worden. (3) Bij aankomst aldaar zal de diagnose geverifieerd moeten worden op de hartcatheterisatiekamer. Na een oplaaddosis thienopyridines en heparine zal met spoed coronairangiografie verricht moeten worden. Ondanks dat (nog) geadviseerd wordt een GPIIb/IIIa receptorblokker te starten voor of tijdens de interventie, wordt dit in ons centrum alleen toegediend in het geval van een gecompliceerde en/of niet volledig geslaagde interventie. Voornamelijk de verhoogde kans op bloedingscomplicaties en hoge kosten geeft aanleiding voor deze terughoudendheid. In ons centrum worden alle interventies gedaan via de transradiale benadering ter beperking van deze bloedingscomplicaties. (4) Indien geïndiceerd zal een primaire PCI met stenting volgen. Een drug-eluting stent is ons inziens slechts geïndiceerd bij patiënten met een hoog risico op het ontwikkelen van restenose, zoals patiënten met diabetes mellitus, kleine vaten en lange vernauwingen. Vooralsnog is er geen plaats voor reperfusieschade-remmende medicatie in de behandeling

van patiënten met een acuut coronair syndroom. (5) Na de interventie en zodra de patiënt klinisch stabiel is, zal verder medicamenteus beleid ingezet worden met een dagelijkse dosering bloedplaatjesaggregatieremmers, thienopyridines, bètablokkers, statines, en 'angiotensine converting enzyme'-remmers (ACE-remmers). Uiteindelijk zal de patiënt na 3-4 dagen naar huis ontslagen kunnen worden bij een ongecompliceerd ziekenhuisverblijf.

Dit proefschrift behelst de evaluatie van enkele strategieën ter verbetering van de behandeling van patiënten met een acuut hartinfarct. Toekomstige behandelingsstrategieën ter verbetering van de ziektevrije overleving zullen gericht zijn op het verdere beperking van de grootte van het hartinfarct door de diagnose vroeg te stellen, op het eerder starten van de behandeling, op beperking van restenose en stenttrombose, en zo mogelijk op regeneratie van myocardiaal (hartspier-) weefsel bij patiënten met grote hartinfarcten.

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