# Treatment Strategies in Interventional Cardiology

Sander IJsselmuiden

# TREATMENT STRATEGIES IN INTERVENTIONAL CARDIOLOGY:

## Direct coronary stenting versus stenting after predilatation

&

## Complete versus culprit revascularization

# Treatment Strategies in Interventional Cardiology

Behandelingsstrategieën in de Interventie Cardiologie

Proefschrift

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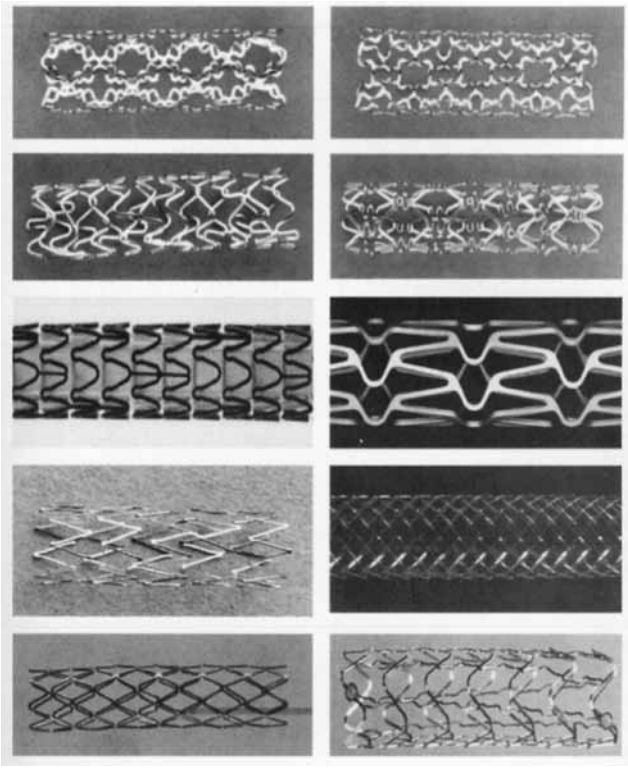
General introduction & Outline of the thesis

In the treatment of patients with obstructive coronary artery disease, myocardial revascularization remains the most important goal as evidence exists that this treatment strategy, even more than prescription of drugs, effectively improves symptoms and prognosis. Besides the classic approach of coronary bypass surgery (CABG), percutaneous coronary intervention (PCI) is at the operators disposal since 1978, (Gruentzig 1978). With the rapidly evolving technology and expanding indications, PCI first rivaled but now has surpassed CABG as treatment of first choice. The development of PCI has stimulated other innovations such as the introduction of the so-called `stent`. Dotter and his colleagues were the first to employ the word `stent` in their description of a technique for the nonsurgical endarterial placement of a tubular coiled wire graft in the peripheral arteries of dogs [1]. Figure 1 shows images of stents used today.

Nowadays, the direct success percentage of PCI in patients with myocardial infarction, stable or unstable angina pectoris with single or multivessel occlusive disease is high (95%). However, on the long-term the success of this new treatment form is still hampered by restenosis in part of the cases. Systematic angiographic follow-up has contributed much to our knowledge and understanding of mechanisms of restenosis.



It is clear that Interventional cardiology -by virtue of its new technologies, potent adjunctive drug therapies (e.g., blockers of the platelet IIb/IIIa receptor), expanding indications, drug-eluting stents and still improving results- has become a dominant discipline at the start of the 21st century. The history of Interventional cardiology has been summarized by Spencer King in an excellent review [2], to which the interested reader is referred for further details.

Figure 1: Ten stent designs evaluated in humans by January 2000.

Figure 2: Normal radiographic anatomy of the left anterior descending coronary artery (LAD) and circumflex artery (CX), as seen in the right (Fig. 2A) and left (Fig. 2B) anterior oblique projection (Fig. 2A), as well as of the right coronary artery (RCA) in the left (fig. 2C) and right (fig.2D) anterior oblique projection.

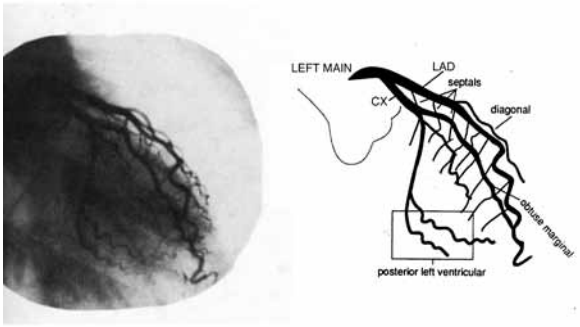



Fig. 2A:

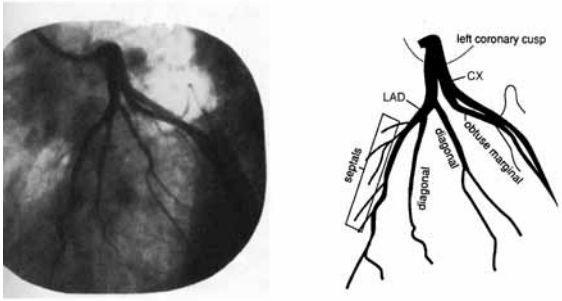



Fig.2B:

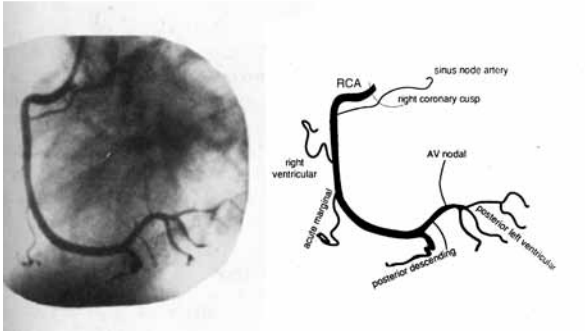



Fig.2C

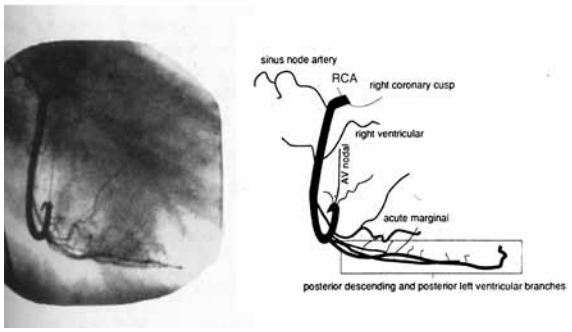



Fig.2D:

Percutaneous coronary intervention

Coronary angiography remains the reference standard for clinical evaluation of patients with known or suspected coronary artery disease. It provides precise information on anatomic distributions of stenotic lesions in large- and medium-sized coronary arteries. The normal radiographic anatomy of coronary arteries is shown in figure 2. To be candidates for coronary angioplasty (figure 3), patients are required to have medically refractory angina, objective evidence of myocardial ischemia and single/ multivessel disease, as characterized by a proximal lesion of more than 50% stenosis which is favorably discrete, subtotal, concentric and noncalcified. Major improvements in equipment and technique have permitted the safe and effective application of coronary angioplasty in patients with far less than these ideal features.

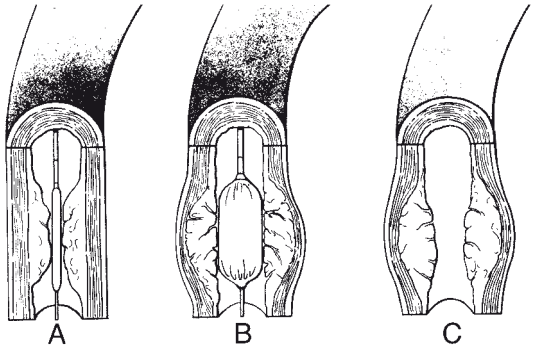



Figure 3: Mechanism of angioplasty. A: deflated balloon positioned across stenosis. B: Inflation of balloon catheter within the stenotic segment causes cracking of the intimal plaque, stretching of the media and adventitia, and expansion of the outer diameter of the vessel. C: After balloon deflation, there is partial elastic recoil of the vessel wall, leaving a residual stenosis of 30% and local plaque disruption that would be evident as `haziness` of the lumen contours on angiography.

Coronary arteries can be approached in several ways. The percutaneous femoral approach is the dominant technique in cardiac catheterization and intervention today. However, the radial approach, mostly used in the OLVG hospital in Amsterdam, the Netherlands, is becoming increasingly popular (figure 4). It has been demonstrated that it has advantages regarding costs and patient comfort. A study by Kiemeneij and colleagues [3] showed that stenting using the radial approach allowed earlier hospital discharge and was associated with decreased in-hospital costs and fewer bleeding complications. However, not in all patients radial approach can be used, especially not in patients who have a negative Allen test suggesting an incomplete palmar arch. Much less common today is the brachial approach. The radial approach has all the advantages of the brachial approach and few of its disadvantages.

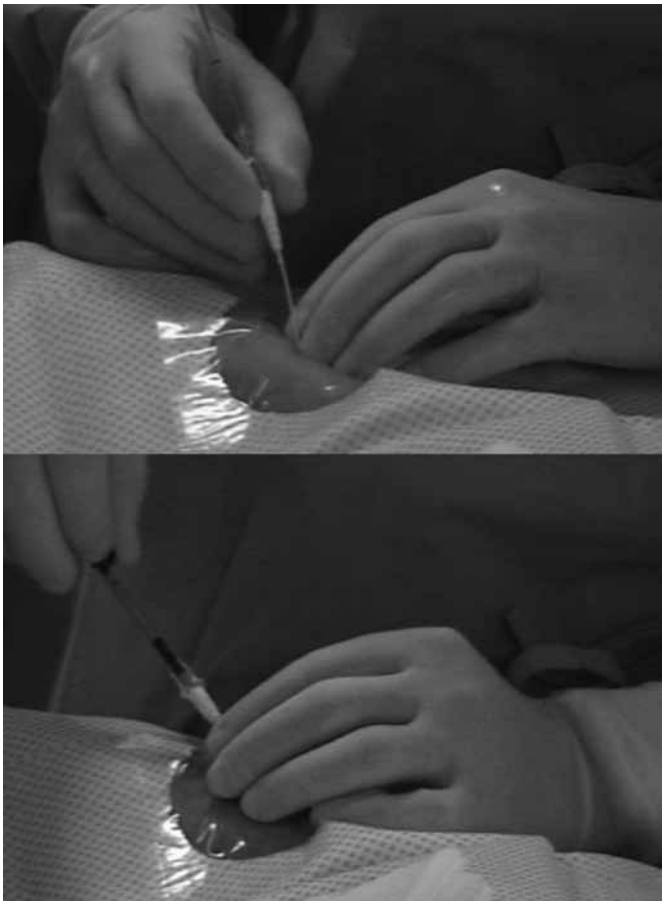


Figure 4: Radial artery cannulation has become increasingly popular due to reduced bleeding complications, hospital stay and therefore medical costs as well as increased patient's comfort compared to the femoral or brachial approach.

A coronary angioplasty sytem consists of three basic components (figure 5):
1. a guiding catheter, which provides stable access to the coronary ostium, a route for contrast administration, and a conduit for the advancement of the dilation equipment. Guiding catheters come with different shapes and outer diameter ranging from 8F (2.7mm, or 0.107 inch) to 6F (1.9mm, or 0.076 inches). Larger guides (9F and 10F) are only used occasionally for certain procedures such as extraction atherectomy. With technical advances even smaller guides have become available (5F and 4F).
2. a leading guidewire that can be passed through the guiding catheter, across the target lesion, and well into the distal coronary vasculature to provide a rail over which a series of therapeutic devices can be advanced.
3. a balloon or stent catheter.
Figure 6 shows the standard stenting procedure in which a lesion is first predilated with a balloon followed by stent placement.

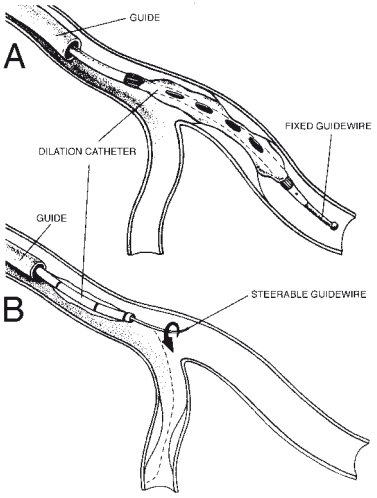



Figure 5: Components of the coronary angioplasty system. The original Gruentzig fixed guidewire balloon (A) is compared with the steerable guidwire system (B). Although both are advanced through a guiding catheter (guide) positioned in the coronary ostium, neither the wire shape nor its orientation could be changed once the original Gruentzig catheter was introduced, whereas the steerable design allows the guidewire to be advanced, withdrawn and reshaped, and steered independently of the balloon catheter to select the desired vessel. Once in place in the distal vessel beyond the target lesion, the guidewire serves as a rail over which the angioplasty balloon or other devices can be advanced.

## Direct stenting versus stenting after predilatation

Considerable advances in coronary stent design and delivery systems have prompted a growing number of interventional cardiologists to attempt the implantation of stents without prior balloon dilatation of the coronary lesion [4-20]. Besides a likelihood of being cost- and time-saving, this strategy offers the hypothetical advantages of causing

less endothelial denudation by stimulating reendothelialization possibly resulting in less vessel wall damage and therefore lower restenosis rates (figure 7). On the other hand, the direct and forceful implantation of the stent through the stenosis may be considerably more traumatic than its insertion after balloon predilatation. The ultimate balance of these opposing effects of direct stenting can only be reliably addressed by properly designed clinical trials. For more background information about direct stenting, the reader is referred to chapter 2, which presents a literature review on this topic.

Culprit versus Complete revascularization

In most intervention centers, percutaneous coronary intervention (PCI) is usually restricted to the vessel thought responsible for ischemia (culprit vessel revascularization). Electrocardiographic changes, scintigraphy, echocardiography and a positive post-infarction exercise in patients with (un) stable and post-infarction angina pectoris can identify the culprit vessel. In addition, results from left ventricular and coronary angiography are often utilized as well to identify the culprit vessel.

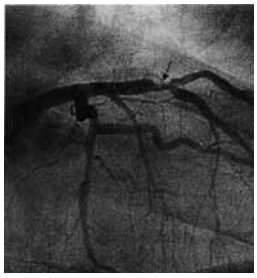


Fig.6A

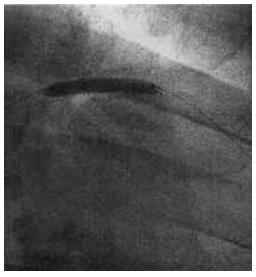


Fig.6B

Fig.6C

Figure 6: Mid-LAD lesion (arrow) with proximal and distal reference vessel diameter of 3.7 mm and 3.1 mm respectively (Figure 6A). It was predilated with a 3.5 mm PCI balloon. An appropriate 4.0mm x 20mm stent is subsequently deployed at 14 atmospheres (Figure 6B). Optimal final result with 0% residual stenosis and an optimal minimal lumen diameter are shown in Figure 6C.

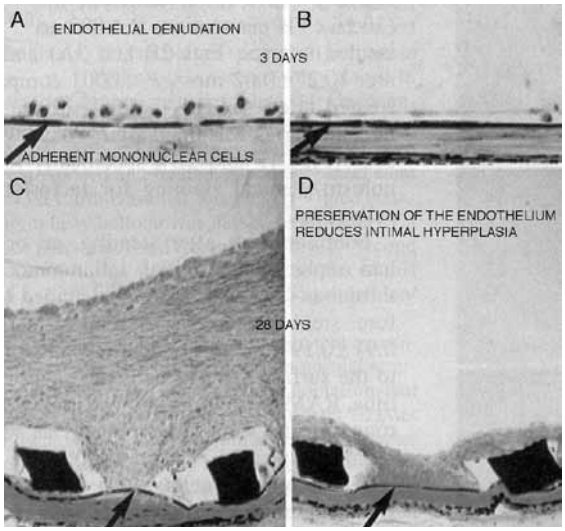



Figure 7: Rationale for the expectation of reduced in-stent restenosis after direct stenting: Direct stenting (B & D) versus stenting after predilatation (A & C) in rabbit Iliac arteries. Initially 83% more adherent monocytes are present in the predilated arteries. After direct stent implantation, preservation of the endothelium under the stent struts results in reduced intimal hyperplasia of 43% at 28 days compared to stenting after predilatation. A study by Rogers et al. published in Circulation 1996; 94; 2909.

Besides obstruction in the culprit vessel, significant lesions in other coronary arteries may be present as well, in which these patients are classified as having multivessel disease (about 5% of total PCI population). Whether more than one vessel will be treated (complete vessel revascularization) depends on the cardiologist, stenosis morphology, extent of jeopardized myocardium, and angiographic results. Retrospective analysis has suggested that long-term prognosis may be favorably influenced by (a more) complete revascularization [20,22,31], which may avoid repeat PCI or coronary artery bypass grafting in a later stage of the `untouched` lesions as are left with the culprit procedure. On the other hand, it has been indicated that the attempt of a complete or more complete revascularization may lead to more peri-procedural complications, longer procedures, higher material consumption, more hospital admissions, higher procedural costs and a higher chance of restenosis [19-30], although the increasing use of intracoronary stents may favorably influence this.

The optimal approach to PCI eligible patients with multivessel coronary artery disease, i.e. culprit versus complete revascularization, is not known at present. So far, no randomized studies have become available comparing the outcome, complications and the degree of revascularization of these two strategies

## Outline of the thesis

The main purpose of this thesis was to investigate the value of two treatment strategies in intervention cardiology, thereby aiming at:

1. Direct coronary stent implantation without prior balloon dilatation.
   - Safety, efficacy and feasibility
   - Predictors of an successful direct stent procedure
   - Angiographic restenosis and long-term clinical events
   - Costs and effectiveness
2. Culprit versus complete revascularization
   - Safety and efficacy
   - Costs and effectiveness

The first two sections of this thesis deal with direct stenting, while the third part investigates complete versus culprit revascularization. The first section includes a literature review and prospective studies investigating direct stenting. The literature review (chapter 2) describes the background, potential advantages and disadvantages of direct stenting. The objective is to review the current available data from studies assessing feasibility, safety, clinical outcome and cost-effectiveness of direct stenting. Chapter 3 describes a registry investigating safety and feasibility of a new stent using smaller guiding catheters (5F) which were introduced via the radial artery. Predictors of a successful direct stent implantation are outlined in chapter 4.

In the second section of the thesis direct stenting is compared to stenting after predilatation in two large randomized studies. Safety, efficacy and procedural costs are described in chapter 5. Long-term angiographic, clinical and economic outcome is

described in chapter 6. The sequential design of the study in chapter 7, which included a non randomized followed by a randomized phase, allowed us to separately 1) examine the 6-month angiographic outcomes of the direct stenting strategy with a new balloon-expandable stent, and 2) compare its effects on clinical events and medical costs up to 9 months with a standard approach of stenting preceded by predilatation, without the confounding influence of protocol-mandated follow up angiography. A subgroup analysis on data from a prospective randomized trial comparing direct stenting with that after predilatation outlined in chapter 8, determines the impact of operator experience on procedural, clinical and angiographic outcome after (direct) stent implantation.
The third part of the thesis (chapter 9) describes a randomized study comparing complete versus culprit revascularization. In the complete revascularization group PCI was attempted on all vessels ≥50% stenosis. It focuses on long-term safety, efficacy and cost of these two approaches.
Chapter 10 provides five case reports on direct stenting with angiographic images which is followed by a summary, abbreviations, acknowledgements, list of publications and a short curriculum vitae of the author.

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# Direct coronary stenting compared to stenting after predilatation, is feasible, safe, and more cost-effective in selected patients with evidence to date indicating similar late outcomes.

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## Abstract:

Objectives: To review the current available data from studies assessing feasibility, safety, clinical outcome and cost-effectiveness of direct stenting.
Background: With technical advances of stent designs and their delivery systems a new strategy has become increasingly popular: direct stent implantation without prior balloon dilatation.
Methods: The Medline database was searched from January 1996 to March 2001 for clinical trials investigating direct stenting using the index terms direct stenting, coronary intervention, PTCA, PCI, angioplasty and ischemic heart disease. Studies were chosen based on the number of patients involved and endpoints mentioned. Data not yet published but presented at recent international meetings was also included. A comparison between direct stenting and stenting with predilatation was performed using for the latter results of the randomized trials supplemented with Benestent II data.
Results: At least 26 studies have investigated direct stenting showing high primary and final success rates with few complications. Direct stenting provides a way to reduce costs, shorten procedural and fluoroscopy times and lower material consumption. Immediate and long-term clinical outcomes appear to be similar to stenting with predilatation. Preliminary results of large randomized trials with angiographic follow-up indicate that restenosis rates are similar to conventional stenting strategies.
Conclusions: Direct stenting compared to stenting with predilatation is feasible, safe, faster and more cost-effective. The evidence to date shows similar late outcomes.

## Introduction

The evolution of coronary intervention from the day angioplasty was first described by Andreas Gruentzig, has been phenomenal. The use of coronary stents, initially recommended as bailout devices has increased exponentially over the last decade[1-3]. The standard deployment procedure of coronary stents requires predilatation of the stenotic lesion by a balloon[4-6]. Now that stent implantation is commonly an elective procedure, predilatation (PREDIL) is only an intermediate step to ensure safe passage across the stenosis and full expansion of the stent. With technical advances in stent design and delivery systems a new strategy has been developed: direct stent implantation (DSI).

DSI is defined as implantation of an intracoronary stent without prior balloon dilatation. This strategy was first reported by Figulla et al. in March 1998[7]. It has been hypothesized that the technique of DSI might be associated with less damage of deeper layers of the vascular wall and reduced endothelial disruption by decreasing the number of balloon inflations and perhaps more important balloon deflations[8-10]. Potential advantages and disadvantages of DSI are outlined in table I.

The question arises whether on balance DSI has advantages over PREDIL in selected patients. We present the first literature study, which reviews the current available data from articles in indexed journals to assess the feasibility, safety, clinical outcome and cost-effectiveness to answer this oft-repeated question.

Table I Potential advantages and disadvantages of direct stenting compared to stenting with predilatation

| (POTENTIAL) ADVANTAGES | (POTENTIAL) DISADVANTAGES |
|---|---|
| • Faster procedures<br>• Less radiation<br>• Less contrast agent usage<br>• Less catheter laboratory time<br>• Reduced ischaemia time due to shorter duration of balloon inflation<br>• Improved patient comfort<br>• No predilatation balloon<br>• More cost-effective<br>• Reduced restenosis rate<br>• Reduced distal embolization in ectatic saphenous graft<br>• Reduced risk of severe dissection by immediately sealing new dissection planes | • Primary/ elective stent indications<br>• Patient selection<br>• Compromized visualization<br>• Compromized precise positioning<br>• Difficulties in sizing of stent diameter and length due to lesion obstruction with absence of distal contrast run-off<br>• Suboptimal guiding catheter support<br>• Failure of crossing the lesion<br>• Partial stent deployment in undilatable lesions<br>• Stent loss or dislodgment at lesion site or guide tip<br>• Stent damage prior to placement<br>• Vessel wall damage and distal embolization because of advancement of a stent in a undilated lesion |

## Stent design and techniques

Improvements in technology have facilitated the strategy of direct stenting. This new therapeutic approach requires a more demanding technique. Prerequisites for direct stent implantation are: experience in sizing of stents, more frequent deep intubation for optimal guiding catheter support and often the selection of stiffer coronary guidewires. In addition, for precise positioning and to minimize the risk of stent loss and failure of crossing the lesion, the following characters are required: stent designs with acceptably low crossing profiles, slippery hydrophilic coatings, stable stent adherence on the balloon and improved flexibility. Moreover, optimal imaging equipment providing adequate visibility of stents and radio-opaque markers are needed.
Techniques for implantation of different stent designs have been previously described[11,12]. In earlier periods 8F guide catheters and over the wire systems with manually crimped stents were used. In more recent studies rapid-exchange systems and smaller diameter guide catheters with lower crossing profile premounted stent delivery systems have been more commonly used. To achieve maximal guiding support the guide may be supported by the opposite aortic wall and or deep coronary intubation may be utilized. This technique is facilitated by the use of smaller outer diameter guide catheters (5F and 6F), so that the guide can be advanced into the coronary artery towards the target lesion. Feasibility and safety of DSI in combination with deep intubation needs further evaluation.
Several stents such as the Multilink (Guidant Inc. Temecula, California), Jostent Flex (Jomed AB, Helsingborg Sweden), the NIR primo stent (SciMed Boston, Scientific, Maple Grove Minnesota), AVE GFX II stent (Medtronic, Minneapolis, USA), the Crossflex stent (Cordis, Johnson & Johnson Company, Warren NJ, USA) and the Blue Medical Devices Genic stent have proved their safety and efficiency particularly for direct stenting[13-17]. As a result of these new technical developments, stents can be delivered into lesions with a more complex morphology.

## Methods

The Medline database was searched from January 1996 to March 2001 for clinical trials and observational studies employing a new treatment of significant coronary stenoses using stents without prior balloon angioplasty. As index terms we used, direct stenting, coronary intervention, PTCA, PCI, angioplasty and ischemic heart disease. Recently completed but not yet published clinical trials have also been included. This yielded 26 studies on DSI[7,15,17,19-41].
To evaluate procedural characteristics of DSI (table II), randomized or prospective observational studies derived from international journals were selected according to the number of patients treated (n >90) and whether the following endpoints were reported: success of DSI, procedural success and occurrence of stent thrombosis. And for most studies: stent dislodgment, dissection and use of additional stents.

For clinical outcome at 1 month (table III), all randomized trials were included. While prospective observational studies derived from international journals were also selected according to the number of patients (n >100) and whether major adverse cardiac events (MACE) were reported.

For studies investigating long-term clinical outcome after DSI the same criteria were used (table IV), but in this case, the criteria 'number of patients' was changed to n ≥ 50 because of the limited number of studies investigating long-term outcome after DSI.
Procedural data and clinical outcome of DSI were compared to PREDIL using the PREDIL results of the randomized trials[19-23] supplemented with Benestent II data[18], to obtain sufficient number of patients. Study design of the Benestent II is a randomized comparison of implantation of a heparin-coated stent with 'plain old' balloon angioplasty in patients who had stable or unstable angina due to denovo lesions; only data of the stent group (with predilatation) was used.
Randomized trials and observational studies comparing DSI with PREDIL which reported procedural time, fluoroscopy time, number of balloons or contrast agent were all used to present an average of these topics (table V).
Data is presented as a mean, median or range. Ninety-five percent confidence intervals (95%_CI) for study means were calculated using Excel 2000 for Windows software.

Table II Key procedural data of direct stent implantation

| Study design: Prospective Observational | Population & Selection criteria | Number patients /lesions | Success DSI % | Success Procedure % | Postdilation % | Stent thrombosis % | Stent dislodgement % | Dissection % | Additional Stent (%) |
|---|---|---|---|---|---|---|---|---|---|
| Pentoussis [25] | AB 2,5,6,8 | 94/ 100 | 97 | 100 | 4.2 | 1.1 | NR | 3.2 | 1.1 |
| Herz [28] | BC 2,5,6,7,8 | 240/ 249 | 93 | 100 | NR | 0 | 0 | 5.6 | 4.1 |
| Hamon [29] | AB 6,7 | 122/ NR | 96 | 100 | NR | 0 | 1.6 | 1.6 | 1.6 |
| Chan [31] | ABC 2,6,7,8,9 | 158/ NR | 98 | 99.3 | 35 | 1.3 | 0 | NR | NR |
| Herz [34] | ABC 5,6,7,8 | NR / 221 | 90 | 100 | NR | 0 | 0 | 7 | 4.5 |
| Veselka [36] | ABC 2,6,7,8 | 90/ 91 | 92 | 100 | 1 | 0 | 0 | 3 | 3 |
| Laarman [24] | BC 2,9 | 250/ 266 | 85 | 99 | 19.9 | 1.6 | 1.6* | 2.6 | 2.6 |
| Taylor [39] | ABC 2,6,7 | 93/ 102 | 96 | 98.9 | NR | 0 | NR | 4.3 | 3.2† |
| Randomized | | | | | | | | | |
| Slide ‡ [21] | BC 1,3,4,5,6,7,8 | 242/ NR | 94 | 99.6 | NR | 0.8 | 0 | NR | 3.7 |
| Carrié § [23] | C 1,2,3,4,5, 6,7,8,9 | 173/ NR | 86 | 98 | 3.4 | 0.6 | 0 | <2 | 9.2 |

Patient population: A acute myocardial infarction B unstable angina C stable angina
Selection criteria: 1 native vessel 2 vessel diameter >2.5mm 3 single lesion 4 de novo lesion 5 lesion length <25mm 6 no severe calcification 7 no severe tortuosity 8 no severe angulation 9 no occlusion
Abbreviations: NR = not reported DSI = direct stent implantation * = 4 stent loss, 2 were retrieved † = 3.2% additional stents and multiple stents for large distal dissection ‡ = publication in press but presented at recent international meeting; results predilatation group: 0.8% subacute stent thrombosis, 0% stent dislodgment § = results predilatation group : 98% procedural success, no postdilatation, stent thrombosis, stent dislodgment or dissection.

## Results:

### Lesion type and patient population

Direct stenting was performed in a wide variety of clinical settings and lesion types: de-novo and restenotic lesions, native vessels as well as venous grafts, simple as well as complex lesions, stable or unstable angina and acute myocardial infarctions. Exclusion

factors used in several studies were severe calcification, tortuosity, angulation and chronic total occlusion. In addition, long lesions (>25mm), small vessels (<2.5mm) and complete coverage of a bifurcation lesion led to exclusion. Possible predictors of failure of DSI are calcified coronary arteries, lesion complexity (long lesion, lesion type C, tortuosity, angulation), lesion location LCX and RCA, distal location and age[7,17,23-24]. Two investigations showed that diameter of the stenosis is not a predictor of failure[17,24]. Reports have suggested that saphenous venous graft stenting without predilatation may decrease procedural complications such as distal embolization, no-reflow phenomenon and periprocedural myocardial infarction (MI)[42].
Because of the high final success rate after predilatation in failed DSI cases it is possible to attempt DSI in nearly all conditions. Although in extreme situations advantages of DSI such as faster procedural time, less contrast and less radiation time are likely to be lost.

Feasibility and safety of direct stenting
Of the twenty-six studies that investigated the feasibility and safety of direct stent implantation we have selected 10 trials to demonstrate key procedural data. Table II outlines the results of these studies.
There was a high success rate of DSI with an average of 93% (95%_CI: 90-96, median 94) varying from 85% up to 98% depending on the patient population, delivery systems and selection criteria used. The remaining patients needed predilatation which were in almost all cases successful (procedural success range: 98-100%). In the PREDIL group procedural success rate ranged from 96-98%. The potential disadvantage 'partial stent deployment' of DSI needs further evaluation because the outcome greatly differed between studies (range: 1 to 35%) and only few studies noted postdilatation. Few dissections were reported for DSI (study mean 3.6; 95%_CI: 2.3-4.9), especially when compared to stenting with predilatation as reported in the Benestent II study (total dissection: 15%)[18]. This advantage of DSI could possibly be due to immediately sealing any new dissection planes. The use of additional stents varied from 1.1 to 9.2% (study mean: 3,6; 95%_CI: 2.1-5.1) which is consistent with the number of dissections. There was almost no stent loss or dislodgment because of DSI (range: 0-1.6%; mean: 0.4%), discarding this potential disadvantage of DSI.

Table III One-month clinical outcome

| Study design<br>Randomized # | Number patients<br>DSI | <br>(PRE) | Death %<br>DSI | <br>(PRE) | Stent thrombosis %<br>DSI | <br>(PRE) | MI Q %<br>DSI | <br>(PRE) | MI non-Q %<br>DSI | <br>(PRE) | TLR %<br>DSI | <br>(PRE) | RE-PTCA %<br>DSI | <br>(PRE) | CABG %<br>DSI | <br>(PRE ) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Slide [21] * | 241 | 120 | 0 | 0 | 0.8 | 0.8 | 0 | 0 | 1.2 | 0.8 | 0.4 | 0 | 0.4 | 0 | 0 | 0 |
| Predict [22] * | 198 | 201 | 0 | 0 | 0.5 | 0.5 | 0 | 0 | 5.6 | 7.5 | 0.5 | 1 | 0.5 | 1 | 0 | 0 |
| Ormiston [20] | 39 | 42 | 0 | 0 | NR | | 2.5 | 0 | 0 | 2 | 2.5 | 0 | NR | | NR | |
| Danzi [19] | 61 | 61 | 0 | 0 | 0 | 1.7 | NR | | NR | | NR | | NR | | NR | |
| Carrié [23] | 173 | 165 | 0 | 0.6 | 0.6 | 0 | 0 ¶ | | 0 | 1.2 | 0 | 0 | 0 | 0 | 0 | 0 |
| Observational DSI | | | | | | | | | | | | | | | | |
| Herz [28] | 240 | | 0 | | 0 | | 0 | | 0 | | 0 | | 0 | | 0 | |
| Hamon [29] † | 122 | | 0.8 | | 0 | | 0 | | 1,6 | | 0 | | 0 | | 0 | |
| Chan [31] † | 158 | | 0.6 | | 1.3 | | 0 | | 0 | | NR | | 0,6 | | 0 | |
| Benestent II [18] | | 413 | | 0 | | 0.2 | | 1.2 | | 0.5 | NR | | | 0.5 | | 0.7 |

Abbreviations: DSI = direct stent implantation PRE = stenting with predilatation TLR = target lesion revascularization RE-PTCA = repeat percutaneous transluminal coronary angioplasty CABG = coronary artery bypass grafting MI = myocardial infarction Q wave and non-Q wave NR = not reported for both groups # = no significant differences between groups for randomized trials * = publication in press but presented at recent international meeting ¶ = not further specified to Q or non-Q wave myocardial infarction † = also patient inclusion of acute myocardial infarction

One month clinical outcome of DSI is compared to PREDIL in table III. Death rate in studies investigating DSI (mean: 0.2%) varied from 0% in studies excluding patients presenting with acute myocardial infarction to 0.6-0.8% in studies which did not exclude these patients. Similar results were found in the PREDIL group (mean: 0.1%) in which patients presenting with acute myocardial infarction were excluded. Acute and subacute stent thrombosis in the studies investigating this topic varied from 0 to 1.3% (mean: 0.4%; 95%_CI: 0.1-0.7). Similar results were found in the PREDIL group (range: 0- 1.7; mean: 0.6; 95%_CI: 0-1.2). Q wave myocardial infarctions (MI Q) after DSI ranged from 0- 2.5% (mean: 0.4; 95%_CI: 0-2.3) compared to 0-1.2 (mean: 0.3; 95%_CI: 0-0.9) in the PREDIL group. The occurrence of non-Q wave (MI non-Q) infarctions were lower in favor of DSI (mean: 1.2; 95%_CI: 0-2.7 versus mean: 2.4; 0-4.9). Although in the randomized trials the incidence of non-Q wave infarctions did not differ significantly between DSI and PREDIL. Similar revascularization rates after DSI were found (mean re-PTCA: 0.3; 95%_CI: 0.1-0.5; CABG: 0%) if compared to the PREDIL group (re-PTCA: 0.3; 0-0.8; CABG: 0.1; 0-0.4).

In the randomized trials comparing DSI with PREDIL, procedural data and short-term clinical outcome did not differ significantly between groups.

The overall conclusion of these trials is that DSI is a safe and effective method for treating coronary artery disease. In appropriate selected cases it has a low rate of procedural failure and complications similar to PREDIL with possibly fewer peri-procedural dissections.

Long-term outcome and restenosis

Coronary stent implantation results in a greater initial lumen gain, but is also characterized by a greater late luminal loss compared to balloon angioplasty[42]. Multiple high-pressure balloon dilatations to prepare the vessel for stent placement and to assure complete stent apposition may increase vessel wall injury and may thus promote the restenotic process[43].

In animal models, when a stent is placed without antecedent balloon denudation, sufficient endothelium remains within the stented segment to allow repopulation with a much-reduced requirement for endothelial proliferation and migration[44]. It is therefore hypothesized that a stent used without predilatation, may provide a means for dilating arteries while avoiding complete endothelial denudation resulting in less neointimal hyperplasia, lower restenosis rates and consequently improved long-term clinical outcome[9,45-47]. However, evidence to date has not confirmed this improvement in clinical and angiographic outcome.

Table IV summarizes late clinical outcomes after DSI. Event rate at six month was low. Few death (mean DSI: 0.5; 95%_CI: 0-1.3 vs. PREDIL: 0.7; 0-1.9), Q- wave myocardial infarction (DSI: 0.9; 0-2.2 vs. PREDIL: 0.6; 0-1.4) and non-Q wave infarction (DSI: 3.3; 0-7 vs. PREDIL: 3.2; 1.7-4.7) occurred after DSI. Revascularization at six month did not differ between DSI (mean re-PTCA: 9.3; 95%_CI: 7-11.6; CABG 2.1; 0-5.1) and the PREDIL group (re-PTCA: 9.2; 8-10.4; CABG: 2.2; 0.5-3.9).

One randomized study[23] showed a difference of MACE in favor of DSI (5.3 versus 11.4%), albeit not significant.

Table IV Six-month clinical outcome

| Study design | Number patients | | Death % | | MI Q % | | MI non-Q % | | TLR % | | RE-PTCA % | | CABG % | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Randomized # | DSI | (PRE) | DSI | (PRE) | DSI | (PRE) | DSI | (PRE) | DSI | (PRE) | DSI | (PRE) | DSI | (PRE) |
| Predict [22] * | 198 | 201 | 0.5 | 2 | 0 | 0 | 6.8 | 8 | 12.1 | 12.4 | 10.8 | 9.5 § | 0 | 0 |
| Danzi [19] | 61 | 61 | 0 | 0 | 0 | 0 | 0 | 0 | 18 | 15 | 10 | 10 | 8 | 5 |
| | | | MACE | | | | | | | | | | | |
| Carrié [23] | 173 | 165 | 5.3 | 11.4 | NR | | NR | | 3.5 | 5.5 | NR | | NR | |
| Observational DSI | | | | | | | | | | | | | | |
| Laarman [24] | 250 | | 2 | | 3.2 | | 8.9 | | 4 | | 8.5 | | 1.2 | |
| Taylor [39] † | 93 | | 0 | | ¶ | | 1.1 | | 0 | | 5,4 | | 1.1 | |
| Oemsrawsingh [15] | 50 | | 0 | | 0 | | 0 | | 8 | | 12 | | 0 | |
| Benestent II [18] | | 413 | | 0.2 | | 1.7 | | 1.5 | NR | | | 8 | | 1.5 |

Abbreviations: DSI = direct stent implantation PRE = stenting with predilatation TLR = target lesion revascularization RE-PTCA = repeat percutaneous transluminal coronary angioplasty CABG = coronary artery bypass grafting MI = myocardial infarction Q wave and non-Q wave NR = not reported for both groups # = no significant differences between groups for randomized trials MACE = major adverse cardiac events (incidence of death, repeat revascularization or myocardial infarction) *= publication in press but presented at recent international meeting § = only non-target re-PTCA counted † = also inclusion of patient with acute myocardial infarction ¶ = not further specified to Q or non-Q wave myocardial infarction

Little is known about the restenosis rate in direct stenting because of the lack of large randomized studies. However preliminary results from 2 randomized trials with 6-month angiographic follow-up indicate that there is no significant difference in the restenosis rate between DSI and PREDIL[19,22]. The rate of restenosis varied from 20.4% to 22.8% in the DSI group versus 20.7% to 20.9% in the PREDIL group.
Evidence to date indicates that DSI leads to similar late outcomes if compared to PREDIL. Large multi-center randomized trials with clinical and angiographic follow-up are being conducted to compare DSI to PREDIL.

Economic considerations
Over the last decade there has been a dramatic rise in the use of coronary stents leading to an increase in costs[48,49]. Several investigators have cautioned that widespread application of these procedures might have a deleterious impact on national health care budgets, thus tempering the general level of enthusiasm for the stenting technique.
An advantage of DSI may be faster procedures with less radiation time, lesser amount of contrast agent used and less material consumption resulting in decreased procedural costs. To define the potential impact of direct coronary stenting on procedural time, fluoroscopy time, balloon usage and amount of contrast agent used we searched for observational or randomized studies comparing DSI with PREDIL. We present an average of all studies investigating these topics although it is difficult to compare among different institutions (Table V).
One observational[31] and five randomized [19-23] comparative studies, which noted an average procedural time of 28.3 minutes versus 36.0 minutes all showed a difference in favor of DSI. This difference in procedural time was significant in three randomized studies [19,20,23].
Three observational[7,17,31] and four randomized[19-22] comparative studies noted fluoroscopy time with an average time of 7.5 minutes versus 10.4 minutes. All seven studies showed a difference in favor of DSI. Two studies showed a significant difference, one randomized[19] and one observational[17].
Two observational[7,17] and two randomized[19,22] comparative studies all showed a decrease in the use of predilatation balloons whereas postdilatation balloons were more commonly used in the DSI group. In several studies it was not defined if the postdilatation balloon was the same as the stenting balloon. The average balloon usage was 0,9 versus 1,5. One randomized study showed a significant difference[21].
Three randomized[21-23] and one observational[14] comparative studies all showed a decreased usage of contrast agent in the DSI group with an average of 148ml versus 170ml. One observational and one randomized study showed a significant difference.
Five studies have translated these results into costs.
Brigouri et al.[30] did a retrospective analysis of 585 successive cases undergoing stent implantation. They identified 185 cases with a favorable anatomy for DSI. In the subset of patients who underwent single vessel stenting the DSI group had a significantly lower procedural cost (1,305 vs. 2,210 Euro).

Table V Procedural data/ resource utilization

| | Number of studies | DSI<br>Range of study means<br>Mean (95%_CI)<br>Median | PREDIL<br>Range of study means<br>Mean (95%_CI)<br>Median |
|---|---|---|---|
| Procedural time (minutes) | 6 (5R,1O) | 7-41<br>28.3 (19.1-37.5)<br>31.5 | 10-59<br>36.0 (22.7-49.3)<br>35.5 |
| Fluoroscopy time (minutes) | 7 (4R,3O) | 5-9.2<br>7.5 (6.4-8.6)<br>7.6 | 6-13.7<br>10.4 (8.4-12.4)<br>11 |
| Balloons (amount) | 4 (2R,2O) | 0.3-1.4<br>0.9 (0.3-1.5)<br>1.0 | 1.3-1.7<br>1.5 (1.3-1.7)<br>1.6 |
| Contrast agent (ml) | 4 (3R,1O) | 135-155<br>148 (139-157)<br>152 | 150-202<br>170 (147-193)<br>163 |

Abbreviations: DSI= Direct stent implantation PREDIL=Stenting with predilatation
R=Randomized O=Observational 95%_CI = Ninety-five % Confidence interval for study means

The NIR future trial[20], a prospective randomized multi-center trial, compared DSI with PREDIL. Equipment cost was significantly lower in the DSI group ($1.199 vs. $1,455).
Danzi et al.[19], showed in a randomized study that the procedural cost were significantly lower for the strategy of DSI than for the conventional approach ($ 2,398 vs. $ 3,776).
Also Carrié et al.[23] proved in a large randomized clinical trial reduced procedural costs in favor of DSI ($ 956.4 vs. $ 1.164.6).
Cotton et al. [50] compared the Benestent II (stent) economic data with direct stenting. Follow-up costs at 1 year in Dutch guilders were Dfl 4500 (DSI) compared to Dfl 9073 (PREDIL).
In summary, it is believed that the direct stent procedure shorten procedural and fluoroscopy time, lowers material consumption and therefore contains procedural costs.

## Conclusions

Now that stent implantation is commonly an elective procedure, predilatation (PREDIL) is only an intermediate step to ensure safe passage across the stenosis and full expansion of the stent.
With advances in stent design and stent delivery systems a new strategy of direct stenting (DSI) has been developed.
In appropriate selected lesions DSI proved to be safe, feasible and an effective method for treating coronary artery disease. It has a low rate of procedural failure and complications similar to PREDIL with possibly fewer peri-procedural dissections.

Several studies have suggested that in DSI there are shorter procedures with less radiation and contrast usage and less material consumption resulting in reduced procedural cost.
Evidence to date indicates that DSI leads to similar late outcomes if compared to PREDIL. Large multi-center randomized trials with clinical and angiographic follow-up are being conducted to compare DSI to PREDIL.
Thus, on balance DSI has advantages over PREDIL in appropriately selected patients: direct stenting compared to stenting with predilatation is feasible, safe, faster and more cost-effective with large clinical trials indicating similar late outcomes.

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# Safe and effective direct implantation of a new stent through 5 French guiding catheters delivery from the radial artery.

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## Abstract

Objectives To evaluate the safety and efficacy of the direct implantation of a new stent via the radial artery through a 5F guiding catheter.
Background Advances in the design of stents and stent delivery systems have facilitated the performance of direct stenting and the use of thinner guiding catheters.
Methods This registry enrolled prospectively 125 patients (147 lesions, 20.4% AHA/ACC class B2/C) who underwent elective percutaneous coronary revascularization procedures with the Blue Medical Devices genic stent for stable or unstable angina between November 2000 and March 2001.
Results Cannulation of the radial artery was attempted in 92.7% and successful in 91.0% of cases. Direct stenting was successful in 88.7% of lesions and procedural success was 99.3%. In-hospital major adverse cardiac events occurred in 1.6% of cases (1 death, 1 semi-urgent coronary artery bypass operation). The final rate of successful stent implantation through 5F guiding catheters was 96.7%. There were no access site-related complications. Failure to cross the lesion occurred in 10% of attempts. At a mean follow up of 7 ± 2.8 months after discharge from the hospital, 79% of patients had remained free of angina, and 89% had remained free of ischemic event.
Conclusions Direct stenting with a new stent design was safe, effective, and could be accomplished via the radial artery through 5F guiding catheters with favorable long-term clinical outcomes.

## Introduction

Advances in the design of stents and stent delivery systems have facilitated the performance of direct stenting [1] and the use of gradually smaller guiding catheters, now as thin as 5F [2-5]. Potential advantages of 5F catheters include lower rates of local vascular complications, smaller blood loss, added support from the highly flexible guiding catheter allowing deep coronary intubation, and less risk of radial artery spasm owing to a favorable guiding catheter/radial artery diameter ratio [2,6].
Advances in stent and guiding catheter technology have reduced access site-related complications, and promoted the use of alternative sites. The radial arterial approach virtually eliminates bleeding complications, is efficient, and preferred by the majority of patients [7]. In selected lesions, direct stenting, compared to stenting with balloon predilatation, can be accomplished safely, more expeditiously and at lower cost [8,9]. Results to date indicate similar rates of restenosis and favorable long-term outcomes [10,11].
The success of direct stent implantation (DSI) depends on the ultra low profile of stent delivery systems and firm support by the guiding catheter to facilitate the stent passage through the lesion. This technique offered an excellent opportunity to examine the performance of a new stent design in combination with 5F guiding catheters in a prospective registry. This report presents its initial results.

## Methods

### Patient population

Between November 2000 and March 2001, 125 patients undergoing elective percutaneous coronary interventions for treatment of stable or unstable angina were prospectively enrolled in the registry. Patients were not included in the registry if they had chronic total coronary arterial occlusions, or if the need for intravascular ultrasound, double balloon techniques or thrombus extraction/atherectomy was anticipated. Proximal vessel tortuosity, lesion calcifications or the presence of a thrombus were not, per se, exclusion criteria.

### Stent design

The Blue Medical Devices Genic™ stent is a 316 L stainless steel slotted tube device, with a strut thickness of 0.10 mm, premounted on a new generation rapid exchange catheter, with two markers at the distal and proximal ends of the stent. The Genic stent is of helical sinusoidal waveform geometry, in which longitudinal connecting elements are placed, optimizing its structural integrity. This unique structure is engineered to combine flexibility with the robustness and radial strength of typical tubular stents. Another characteristic of the Genic stent is a new, advanced mounting and crimping technology, which ensures optimal attachment of the stent to the balloon and a smooth, < 1.0 mm crossing profile. The device is available in 2.5, 3.0, 3.5, 4.0 mm diameters

and 10, 14, 18, 22, 28 mm lengths. The nominal stent diameter is obtained at 6 atm, and the rated burst pressure is 16 atm. The low crossing profile, unlimited pushability, flexibility and trackability ensuring precise navigation and optimal placement, combined with tight stent-balloon attachment for safe delivery and, if needed, retrieval, makes this device especially suitable for DSI.

Percutaneous coronary interventions

Catheterization attempts via the radial arterial access route were made in all patients with a positive Allen test in either upper extremity. In patients with a bilaterally negative test, catheterization was performed from brachial or femoral sites. A variety of 5F guiding catheters with appropriate curves were used. The target lesions were crossed with a 0.014 inch coronary guide wire. Contrast was injected manually in all cases. The Blue Medical Devices Genic stent was used in all patients. An optimal procedural result was defined as a residual stenosis < 25% of the luminal diameter by quantitative angiographic analysis.

Anti-thrombotic regimen

Aspirin, 500 mg i.v. was administered before, and clopidogrel, 300 mg orally, was administered after the procedure to all patients. Heparin, 10.000 U, was given in an intravenous bolus at the beginning of the procedure, followed by additional hourly boluses of 5000 U. Platelet IIb/ IIIa inhibitors were not used. After the procedure all patients received 75 mg of clopidogrel daily for 1 month. Aspirin, 100 mg daily, was continued for at least 6 months.

Quantitative angiographic analysis

Quantitative computer assisted angiographic measurements were performed in all patients, before and after the procedure, under standardized conditions. The angiograms were recorded just before and immediately after stent implantation. All coronary angiograms were analyzed on-line by a Poly Diagnost Digital Cardiac Imaging System (Philips, Best, The Netherlands). The diameter of the reference vessel, minimal luminal diameter and percent diameter stenosis were measured. Lesion types were graded according to the American College of Cardiology/ American Heart Association lesion characteristics classification. Tortuosity was defined as the presence of 2 or more bends > 45° to the lesion. Procedure-related arterial dissections of any type were also noted.

Procedural endpoints

The primary endpoint of this trial was procedural success, defined as TIMI grade 3 flow [12], and successful stent deployment, with a final percentage diameter residual stenosis < 25% within the stented segment measured by quantitative coronary angiography. Secondary endpoints included failure of DSI, need for postdilatation, dissection, need for deep intubation, poor guiding catheter support, stent loss, stent thrombosis and occurrence of friction during passage of stent through lesion. Clinical follow up began from the time the patient left the catheterization laboratory. All major adverse cardiac

and cerebrovascular events and complications related to the catheterization access site were recorded.

### Measures of long-term clinical outcome

All patients were interviewed personally or by telephone six month after their discharge from the hospital. Major adverse cardiac and cerebral events were defined as death from any cause, myocardial infarction, coronary artery bypass grafting, further coronary revascularization, whether of the target lesion/vessel or not, and cerebral vascular accident. Revascularization of the target lesion was defined as angioplasty or bypass surgery performed for restenosis of the target lesion associated with recurrent angina, or objective evidence of myocardial ischemia, or both. Diagnosis of myocardial infarction was based on prolonged typical chest pain and documentation of new pathological Q-waves >0.03 s in duration, or as a rise in creatine kinase enzyme or its MB fraction above twice the upper limit of normal value, associated with prolonged chest pain. Measurements of serial enzymes and troponin levels, or the recording of electrocardiograms were only performed in presence of signs or symptoms consistent with a myocardial ischemic event. Anginal class was graded according to the Canadian Cardiovascular Society classification.

### Statistical analysis

The data are presented as means ± standard deviation for continuous variables, and percentages for categorical variables. Statistical tests were carried out two-tailed at the 5% level of significance.

Table I Baseline characteristics of the patient population (n=125)

| | |
|---|---|
| Age, y (mean±SD) | 61 ± 11 |
| Men | 85 (68) |
| Diabetes mellitus | 7 (5.6) |
| Hypertension | 45 (36) |
| Hypercholesterolemia | 68 (54.4) |
| Current smoking | 19 (15.2) |
| Family history of coronary artery disease (%) | 40 (32) |
| Indications for coronary intervention | |
| Stable angina | 85 (68) |
| Unstable angina | 40 (32) |

Except for age, all values indicate number (%) of patients

Table II Angiographic findings and characteristics of 147 coronary artery lesions

| | |
|---|---|
| Lesion Site (%) | |
| Left anterior descending coronary artery | 40 |
| Left circumflex coronary artery | 21 |
| Right coronary artery | 35 |
| Left Main coronary artery | 2 |
| Vein graft | 2 |
| Lesion AHA/ACC type (%) | |
| A | 17 |
| B1 | 53 |
| B2 | 24 |
| C | 6 |
| Lesion Morphology (%) | |
| Calcification | 16 |
| Evidence of Thrombus | 8 |
| Proximal tortuosity | 17 |
| Baseline TIMI flow (%) | |
| I-II | 11 |
| III | 89 |
| Reference vessel diameter, mm (mean±SD) | 2.8±0.6 |
| Pre-procedure MLD, mm (mean±SD) | 0.8±0.4 |
| Pre-procedure % stenosis, (mean±SD) | 70±4 |
| Post-procedure MLD, mm (mean±SD) | 2.6±0.4 |
| Post-procedure % stenosis, (mean±SD) | 12±9 |

AHA/ACC = American Heart Association/American College of Cardiology

## Results

The baseline characteristics of the patient population are presented in table I, and the angiographic findings and baseline characteristics of the 147 coronary lesions treated are listed in table II. Among the 125 patients, 105 underwent treatment of a single lesion, 18 had 2, and 2 patients had 3 lesions treated. Radial artery cannulation was attempted in 92.7%, and successful in 91% of cases. The brachial and femoral approaches were used in 2.4% and 4.8% of cases, respectively.

The procedural results are presented in table III. DSI was successful in 88.7% of lesions. In case of failure of direct stenting, balloon predilatation was performed with an overall procedural success rate of 99.3%. One patient died of cardiogenic shock and respiratory failure 2 days after the index procedure. This patient had been admitted to the intensive care unit with endstage heart failure, renal failure and recurrent ventricular tachycardia. An autopsy was refused. This death was not considered procedure-related since the patient entered the laboratory in severe cardiac failure. The success rate of stent placement through 5F guiding catheters was 96.7%. Deep intubation of the guide into the target vessel was utilized in 33.6% of procedures without coronary dissection. One

patient required semi-urgent coronary artery bypass graft surgery after attempts to cross a left main coronary artery lesion had failed. Local or systemic stent embolization did not occur, and no patient suffered a myocardial infarction. There were no peripheral access site-related complications.

Table III Procedural results

| | |
|---|---|
| Procedural success | 99.3 |
| Procedural success via 5F guides | 96.7 |
| Successful direct stent implantation | 88.7 |
| Failure to cross lesion | 9.9 |
| Additional stent for dissection | 6.8 |
| Postdilatation | 6.8 |
| Major adverse cardiac events | 1.6 |
| Guiding catheter performance | |
| Poor guide support | 7.2 |
| Cannulation failure | 3.2 |
| Defective catheter | 0.8 |

All values represent % of patients

The Genic stent was easily passed through all 5F guiding catheters, failed to reach the lesion in 1.4%, and failed to cross the lesion without predilatation in 10% of cases. Friction during passage of the stent through the lesion was reported as "none" in 65%, "moderate" in 21%, and "pronounced" in 4% of attempts. A variety of stent diameters and lengths were used. A total of 156 stent systems were used, 10 (6.8%) of which were needed for management of dissection following a first stent implantation. The average number of stents used was 1.25 per patient (table IV).
Clinical outcomes were known for 97% of patients at a mean follow-up of 7 ± 2.8 months. Table V lists the major adverse cardiac events and anginal status recorded after discharge of the patients from the hospital.

Table IV Device utilization

| Mean number of item per patient (total) number) | |
|---|---|
| Stent systems | 1.25 (156) |
| Balloons | 0.35 (44) |
| Guiding catheters | 1.3 (162) |
| Guide wires | 1.2 (147) |
| Stents | 1.2 (146) |
| Stent length (%) | |
| > 22 mm | 12 |
| 14-18 mm | 26 |
| 10-14 mm | 35 |
| < 10 mm | 27 |
| Stent diameter (%) | |
| 2.5 mm | 28 |
| 3.0 mm | 45 |
| 3.5 mm | 23 |
| 4.0 mm | 4 |

Table V Long-term clinical follow-up of 121 patients (97% of original population)

| Follow-up duration, months (mean ± SD) | 7.6±2.8 |
|---|---|
| Major adverse cardiac event | |
| Myocardial infarction | 2 (1.7) |
| Coronary artery bypass surgery | 5 (4.1) |
| Further coronary artery revascularization | 10 (8.3) |
| Target lesion revascularization | 6 (4.8) |
| Any major adverse cardiac event | 16 (13) |
| Angina pectoris-free status | 96 (79) |

Except for follow up duration, all values indicate numbers (%) of patients and are rank ordered. 3 patients had >1 major adverse cardiac event

## Discussion

The initial results of this prospective registry indicate that DSI with the Blue Medical Devices Genic stent, delivered from the radial route via 5F catheters, was safely accomplished with a high procedural success rate, in a mostly unselected patient population. The use of 5F guiding catheters was associated with no access site-related complications or radial artery spasm. Furthermore, the clinical results at a mean of 7 months after hospital discharge were favorable, with absence of angina in 79% of patients and an 86% ischemic event-free survival. Considering the liberal selection criteria used, these results can probably be extrapolated to a general patient population undergoing elective percutaneous coronary revascularization procedures.

Despite variable degrees of guiding catheter support, the success of DSI was similar to that observed in previous studies using thicker guides. This success rate may be attributable, in part, to the technique of deep coronary intubation, used in a high proportion of cases. Particularly noteworthy was the absence of guiding catheter-related dissection complicating this deep intubation, probably because of the flexibility of the catheters. The assumption that thinner guiding catheters offer weak support appears invalid since the technique often reliably stabilized the catheter. The feasibility of 5F guided interventions has been confirmed in studies of other devices [2].
Successful DSI hinges on the availability of low-profile stent delivery systems and reliable guiding catheter support to allow passage of the stent through the lesion. In these technically more challenging conditions, the performance of the Genic stent in passing through 5F guides and crossing the lesion was high. Friction during passage of the stent through the lesion was reported as "pronounced" in only 4% of cases. Procedural complications and long-term clinical outcomes were similar to previous studies of DSI using larger guides [9-11,13].

Limitations of the study
This registry was a non-randomized study from a single center. No comparison was made with larger guiding catheters. In addition, most, though not all procedures could be performed from the radial approach. Furthermore, the radial pulse was not systematically examined, which may have minimized the incidence of peripheral arterial access-related complications. Finally, serial enzymes and troponin levels were measured and electrocardiograms recorded only when a myocardial infarction was suspected, which may explain the unusually low incidence of periprocedural myocardial infarctions.
In conclusion, this registry documents the high compatibility of the Blue Medical Devices Genic stent with 5F guiding catheters inserted via the radial route. This combination was safe and effective in the performance of DSI, and was associated with a high procedural success rate and favorable clinical outcomes up to a mean of 7 months after the procedure.

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# Direct coronary stent implantation: safety, feasibility, and predictors of success of the strategy of direct coronary stent implantation

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## Abstract

Objectives: This prospective study was designed to evaluate the feasibility, safety, predictive factors of success, and 6 month follow-up of stent implantation without balloon predilatation ("direct stenting") in 250 patients undergoing elective stent implantation.

Background: Balloon dilatation prior to stent implantation was a prerequisite to facilitate passage and deployment of the stent. Stent technology has changed tremendously resulting in stents with improved properties, which may allow stent placement without prior balloon dilatation.

Methods: Patients with coronary lesions suitable for elective stent implantation were included in this trial. Coronary interventions were undertaken predominantly via the transradial route using 6F guiding catheters. Direct stent implantation was attempted using AVE GFX II coronary stent delivery systems. Upon failure, predilatation was undertaken before reattempting stent implantation. Patient data and EKGs were obtained from case records and from personal or telephone interviews 6 months after the procedure. Values are presented as mean ± standard deviation. Student's t-test, two tailed at 5% level of significance was used to compare the difference of two means. Multivariate logistic regression analysis was performed to establish predictive factors for failure of direct stenting.

Results: Two-hundred and sixty-six direct stent implantations were attempted in 250 patients. Direct stenting was successful in 226 (85%) cases. Out of 40(15%) cases where direct stenting failed, balloon predilatation facilitated stent implantation in 39. In one lesion, stent implantation was not possible despite adequate predilatation. Predictive factors for failure of direct stenting on multivariate analysis were Circumflex lesions ($p<0.01$), complex lesions ($p<0.01$), and longer stents ($p<0.001$). Minimal luminal diameter and percentage diameter stenosis of lesions in the successful and the failure group were not significantly different ($0.94 \pm 0.39$mm vs. $0.84 \pm 0.41$ mm (p=NS), and $70.2 \pm 11.2$ vs. $73.2 \pm 11.2$ (p=NS)). Stent loss occurred in five (2.0%) cases with successful retrieval in four. One stent was lost permanently in a small branch of the radial artery. Post-PCI myocardial infarction occurred in four (1.6%) patients. There were no other in-hospital events.

Follow-up after 6 months: Six month follow up information was obtained in 99% of patients. Sub-acute stent thrombosis was noted in four (1.6%) cases. Target vessel related myocardial infarction rate was 3.2%, of which half was caused by subacute stent thrombosis. The overall reintervention rate (CABG ánd PCI) was 9.7%. Target lesion revascularization by PCI occurred in only 4.0%. At 6 months overall mortality was 2.0%, of which 1.2% was due to coronary events.

Conclusions: Direct stent implantation is safe and feasible in the majority of cases with low rate of complications. Unfavorable factors include circumflex lesion, more complex lesion morphology, and increasing length of stent. Severity of stenosis does not appear to be of predictive value. Long-term outcome is favorable with a low target lesion revascularization rate.

## Introduction

Intracoronary stent implantation following balloon angioplasty was initially undertaken as a bail-out procedure to deal with flow-limiting dissections resulting from balloon dilatation. The superiority of elective stent implantation compared to balloon angioplasty alone in terms of restenosis has been well documented in the Benestent and Stress trials (1,2). Although these trials dealt with highly selected patient populations, elective stent implantation is now increasingly undertaken in various patient subsets (3,4).
Balloon dilatation prior to stent implantation was usually a prerequisite to facilitate passage and deployment of the stent. This was particularly important with the first generation high profile, hand-mounted or sheath-protected stents. In recent years stent technology has improved tremendously resulting in systems with improved stent fixation, profile, trackability and flexibility. This could allow stent placement without prior balloon dilatation ("direct stenting") (5,6).
The aim of this prospective trial was to evaluate the safety, feasibility, predictors of success, and long-term clinical outcome of direct coronary stenting using the AVE GFX II coronary stent system.

## Methods

### Patients

We performed a prospective nonrandomized trial of direct stenting with the AVE GFX II coronary stent system in 250 consecutive patients. The procedures were performed by five operators (GJL, TSM, FK, TS and RvdW).
Included were patients with symptomatic and objective evidence of myocardial ischemia and angiographic evidence of significant CAD requiring PCI. Patients were all selected for elective stentimplantation. Excluded were patients with small target vessels (less than 2.25 mm in diameter), diffuse disease distal to the target segment that may limit coronary flow with increased risk of subacute thrombosis, and chronic total occlusions.

### Definitions

Successful direct stenting was defined as stent placement without prior balloon dilatation; direct stenting was considered a failure when predilatation was needed for stent placement. Successful final stent placement was defined as adequate stent positioning with ≤ 30% diameter residual stenosis (quantitative measurement), TIMI grade III flow and the absence of in-hospital death, Q-wave MI, urgent repeat PCI, or urgent CABG. Definition for myocardial infarction: the presence of at least two of the following: 1) An episode of prolonged chest pain, 2) Serial enzyme pattern, typical of myocardial infarction, with at least one enzyme exceeding twice the upper limit of normal, and 3) New Q-waves. Vascular complications were defined to have occurred if blood transfusions and/or surgical interventions were required. Procedural times were measured as the time intervals between sheath insertion and guiding catheter removal

after PCI. Fluoroscopy times were automatically produced by the Philips Poly Diagnost (C2) Digital Cardiac Imaging System.
Learning curve: Failure rate of direct stenting during the first half of the study was compared to that during the second half of the study.

Intracoronary stent implantation techniques
Coronary angioplasty and intracoronary stent implantation were performed using standard percutaneous techniques via the radial or femoral artery (3). Only 6 French guiding catheters with appropriate curves were used. The AVE GFX II
stent system was used in all cases. The decision regarding the diameter and length of stents was at the discretion of the operator. The need for deep intubation to improve guiding catheter support, the degree of friction during stent positioning, and the adequacy of distal vessel opacification were noted. Patients were discharged within 24 hours of the procedure.

Medical therapy
All patients received 500mg aspirin i.v. and 10.000 IU of Heparin i.v. before the procedure. After the procedure Ticlopidin p.o. was started with 500mg and continued for 30 days (250mg per day). Aspirin 100mg p.o. was continued after the procedure. No Heparin was administered after PCI as routine.

Coronary angiography
Lesion types were noted according to the American College of Cardiology/American Heart Association lesion characteristics classification. Dissections (of any type) after PCI were also noted. On-line quantitative coronary artery analysis was performed with the Philips Poly Diagnost (C2) Digital Cardiac Imaging System and the integrated analysis program before and after the procedure under standardized conditions.

Events
Events, including death, MI, CABG, repeat PCI, stent loss and subacute stent thrombosis were noted during hospital stay and after 6 months follow-up.

Six month follow-up
Patient data, including EKGs were obtained for review from case records from our institution or from other hospitals. In addition, patients were interviewed personally or by telephone 6 months after the procedure.

Statistical analysis
Descriptive statistics (mean ± standard deviation for continuous variables, percentages by category for categorical variables) were used to summarize data. Differences between group means were analyzed using the unpaired student's t-test. All statistical tests were carried out two-tailed at the 5% level of significance. A new ordinal was created comprizing the values one, two, and three corresponding to the three categories

of lesion morphology. The relationship between lesion morphology and success of direct stenting was estimated using logistic regression analysis, with the ordinal variable as the dependent variable. Variables, which were associated with the outcome of successful direct stent implantation ($p < 0.10$), were included in a multivariate logistic regression model to establish their predictive value for failure of direct stenting. Analyses were performed using SPSS 8.0 for Windows statistical software.

Table I. Clinical characteristics.

| | | |
|---|---|---|
| Age (years)* | | 62.9 ± 11.4 |
| Male | | 176 (70.4%) |
| Angina pectoris class (CCS) | 1 | 10 (4%) |
| | 2 | 71 (28.4%) |
| | 3 | 83 (33.2%) |
| | 4 | 86 (34.4%) |
| History of hypertension | | 98 (39.2%) |
| History of hypercholesterolemia | | 143 (57.2%) |
| Family history | | 112 (44.8%) |
| Smoking (Current) | | 131 (52.4%) |
| Previous myocardial infarction | | 87 (34.8%) |
| History of diabetes | | 33 (13.2%) |
| Previous PCI | | 50 (20%) |
| Previous CABG | | 27 (10.8%) |

*Continuous variables are presented as mean values ± standard deviation (SD).
Numbers and percentages of patients.

Table II. Angiographic characteristics.

| | | | |
|---|---|---|---|
| Number of diseased vessels* | 1 | 127 | (50.8%) |
| | 2 | 77 | (30.8%) |
| | 3 | 46 | (18.4%) |
| Target vessel# | RCA | 83 | (31.2%) |
| | LCx | 42 | (15.8%) |
| | LAD | 111 | (41.7%) |
| | DIAG | 10 | (3.8%) |
| | LM | 5 | (1.9%) |
| | SVG | 15 | (5.6%) |
| Lesion Morphology (ACC/AHA)# | A | 71 | (26.7%) |
| | B1 | 111 | (41.7%) |
| | B2 | 42 | (15.9%) |
| | C | 42 | (15.9%) |
| Lesion Calcification# | | 27 | (10.2%) |

*Numbers and percentages of 250 patients.
#Numbers and percentages of 266 lesions.

## Results

### Patients

Baseline characteristics of 250 patients (266 lesions) are presented in Tables I and II. One-third of the patients had CCS class IV angina pectoris, half of them had multivessel disease, and one-third ACC/AHA type B2 or C lesions.

### Procedural characteristics

6 French guiding catheters were used in all cases. The use of larger bore guides was not required in any patient. The transradial approach was performed in 82.7% of cases. Direct stenting was successful in 226 lesions (85%). In the 40 lesions, in which direct stenting failed, stent implantation after predilatation was successful in 39, resulting in a final success rate of 99% (Table III).

Table III. Successful versus failed direct stenting.

| | Direct stent successful | Direct stent failure |
|---|---|---|
| Target lesions | 226 (85.0%) | 40 (15.0%) |
| Lesion calcification# | 22 (9.7%) | 5(12.5%) (p=0.64) |
| Minimal lumen diameter (Pre-PCI) (mm) | 0.94 ±0.39 | 0.84±0.41 (p=0.08) |
| Reference diameter (mm) | 3.14 + 0.55 | 3.15±0.53 (p=0.86) |
| % Diameter stenosis | 70.2 ± 11.2 | 73.2±0.53 (p=0.09) |
| Stent diameter (mm) | 3.19 ± 0.27 | 3.22±0.3 (p=0.65) |
| Stent length (mm) | 15.8 ± 4.9 | 18.3±6.0 (p<0.0001) |
| Deep intubation# | 49 (21.7%) | 26(65%) (p<0.0001) |
| Fluoroscopy time (min)* | 6.8 ± 4.9 | 13.0±9.3 (p<0.0001) |
| Duration of procedure (min)* | 24.0 ± 13.2 | 39.0±20.1 (p<0.0001) |
| Volume of contrast (ml)* | 154.5 ± 52.9 | 218.7±73.0 (p<0.0001) |

#Numbers and percentages of 266 lesions. *Per procedure. Continuous variables are presented as mean values ± standard deviation (SD).

Although there was a trend for better success in the transradial group compared to the transfemoral group, this did not reach statistical significance. The success rates of direct stenting according to lesion morphology, target vessel, and stent length are presented in Table IV. Multivariate analysis revealed that predictive factors of failure were LCx lesions ($p<0.01$), complex lesions ($p<0.01$), and longer stents ($p<0.001$).
The failure rate of direct stenting in the first half of the study period was 20.1% versus 9.9% in the second half. Deep intubation of the guiding catheter was necessary in 49 (21.7%) cases to facilitate direct stent implantation. In the failure group deep intubation was undertaken in 65% of cases.

Table IV. Predictors of success of direct stenting.

| | Total n | Success n (%) | p-value |
|---|---|---|---|
| Lesion morphology A | 71 | 66 (93.0) | P for trend <0.01 |
| B1 | 111 | 95 (85.6) | |
| B2 | 42 | 33 (78.6) | |
| C | 42 | 32 (76.2) | |
| Stent length* ≤ 12 | 131 | 120 (91.6) | p for trend |
| 18 | 102 | 87 (85.3) | < 0.0001 |
| 24 | 25 | 15 (60) | |
| 30 | 8 | 4 (50) | |
| Target vessel LM | 5 | 5 (100) | |
| SVG | 15 | 14 (93.3) | |
| LAD/DIAG | 121 | 109 (90.0) | |
| RCA | 83 | 69 (83.1) | |
| LCx | 41 | 28 (68.3) | P = 0.002 |

Univariate logistic regression analysis.
*Initial stent used for the direct stenting attempt.

Moderate to severe friction in crossing the lesion was experienced in 56 (24.8%) cases. Impaired distal vessel opacification was noted in 7.5% of direct stent cases. However, this did not result in imperfect positioning of stents. Following direct stent placement, a total of seven (2.6%) dissections were seen, all of which were treated with additional successful stent implantations.
Post-stent balloon dilatation was performed in 45 cases (19.9%) after successful direct stenting. In the failed direct stent cases post-stent dilatation was performed in 5.1%.

Stent loss
Stent loss was noted in 4 cases of direct stenting. In three patients the stent was successfully retrieved and in one patient the stent was lost permanently in a small side branch of the radial artery without clinical sequela. In one patient a stent was lost despite adequate predilatation but was retrieved.

Fluoroscopy and procedural times
In the successful direct stent group mean fluoroscopy time was 6.8±4.9 min. versus 13.0±9.3 min. in the failure group. Mean procedural times were 24.0±13.2 min. and 39.0±20.1 min., respectively (Table III).

In hospital events
Four patients experienced myocardial infarction, two Q-wave infarctions and two non Q-wave infarctions. There was no other in hospital complications.

Vascular access site complications
There were 5 cases of access site complications. There was one death due to this complication. All vascular complications were from the femoral access site. The transradial procedures were not associated with access site complications.

### Subacute stent thrombosis

Subacute stent thrombosis occurred in four cases (1.6%), three in the successful and one in the failure group.

Table V. Six month follow-up.

| | |
|---|---|
| *Stent thrombosis | 4 (1.6%) |
| Target related MI | 8 (3.2%) |
| Total MI | 22 (8.9%) |
| Target related PCI | 10 (4.0%) |
| Total PCI | 21 (8.5%) |
| Emergency CABG | 0 (0.0%) |
| Elective CABG | 3 (1.2%) |
| Death due to coronary event | 3 (1.2%) |
| Death due to access site complications | 1 (0.4%) |
| Death due to carcinoma | 1 (0.4%) |

*Numbers and percentages for 250 patients
Numbers and percentages of 248 patients.

### 6 Month follow up data

Complete follow up data was available for 248 (99%) patients. The results are summarized in Table V. There were 5 deaths. Two patients died within 48 hours after the procedure. One death was due to delayed but catastrophic bleeding from femoral puncture site resulting in hypovolaemic shock and death. The other death was due to myocardial infarction related to the target vessel; however post mortem study revealed that the infarction had been due to rupture of a previously non significant plaque proximal to the stented target lesion. There was no evidence of stent thrombosis or dissection. Three deaths were noted between three to six months after the coronary intervention. One death was due to disseminated small cell carcinoma of the lung. Post mortem examination in this patient revealed a patent stent. One patient died after suffering an extensive anterolateral myocardial infarction. Post mortem examination revealed rupture of a plaque in the left main stem, which was not present on the previous coronary angiography. An 84 year old man who underwent direct stent implantation of the unprotected left main stem three months earlier was admitted with recurrent ventricular arrhythmia and rapid deterioration possibly due left main stem restenosis. No post mortem examination was performed in this case. Overall target lesion rePCI for instent restenosis was 4.0%.

## Discussion

As the technique of direct stenting is more demanding, prerequisites are experience in sizing of stents, the technique of deep intubation to improve guiding catheter support, and exact positioning of stents. In addition, low profile stent delivery systems with minimal risk of stent dislodgment, optimal imaging equipment, providing good visibility of stents and anatomical landmarks are needed for precise positioning.
Potential disadvantages of direct stenting are higher failure rates in more complex lesion morphology, compromized stent positioning, difficulties in sizing of stent diameter ánd length due to lesion obstruction and diminished contrast run-off, the need for better catheter support, partial stent deployment in "undilatable lesions", stent loss at lesion site or guide tip and stent damage prior to placement. Advancement of a stent in an undilated lesion may result in vessel wall damage and distal embolization.
Potential advantages of direct stenting are faster procedures with less radiation and contrast, reduced ischemia times, less material consumption and cathlab time, leading to increased safety, improved patient comfort, and lower costs. Moreover, less vessel wall trauma by decreasing the number of balloon inflations and, perhaps more importantly, balloon deflations, could translate into improved long-term outcome by the reduction of restenosis.
In the present study using one type of stent system, success of direct stenting was 85% in an almost unselected patient population. Failure of direct stenting was not harmful to patients and successful stent implantation could be performed after predilatation in all but one patient, resulting in a 99% final success rate. There was a clear learning curve: the failure rate of direct stenting in the first half of the study period was 20.1% versus. 9.9% in the second half. Probably the most important factor in the learning curve is guiding catheter selection and manipulation. To achieve maximal guiding catheter support the guide is supported by the opposite aortic wall and/or by deep Cannulation. The latter technique is facilitated by the use of small bore catheters (5 and 6 FR), so that the guide can be advanced into the coronary artery up to the target lesion. As long as the guide is advanced over the balloon/stent catheter this maneuver is safe.
The problem of partial deployment of a stent in an "undilatable lesion" was not encountered. Analysis per coronary artery revealed that lowest success rates were found in the LCx (68.3%) and the RCA (83.1%). Success rate of direct stenting decreased with lesion complexity and stent length (representing lesion length). These findings could be taken into account when patients are selected for stent implantation. Percentage diameter stenosis, minimal luminal diameter and stent diameter were not predictive of success of direct stenting. Direct stenting of graft lesions has
been advocated to diminish the risk of embolization (7). We attempted direct stenting in 15 cases with success in all but one. We performed this approach in five patients with left main stem stenosis. It is conceivable that reducing ischemia time is especially beneficial in this situation.
This study is another example of the potentials of 6 French guiding catheters in PCI. High success rates were achieved using these catheters in the demanding technique of

direct stent implantation. Furthermore, in combination with the transradial approach, vascular access complications were greatly diminished. Fluoroscopy and procedural times in the patient group where predilatation was needed, were similar to those found in a recent series of 900 PCI patients in our institution (3), indicating that even in case of initial failure of direct stenting, fluoroscopy and procedural times still are relatively short. The long-term outcome was favorable with an uneventful 6 month course in 80% of this patient population, subjected to minimal selection criteria. Therefore, these results could be translated to the general PCI population. In particular, the target lesion revascularization rate was surprisingly low. It may be hypothesized that the technique of direct stenting is associated with less damage of deeper layers of the vascular wall and reduced endothelial disruption, resulting in decreased restenosis rates. This hypothesis can only be tested in a randomized prospective angiographic study.

Study limitations

Although this prospective study has favorable success and event rates, proper comparisons can only be made in a randomized trial, especially with regard to the long-term outcome in terms of events and angiographic restenosis. For this reason we are conducting such a trial using the latest generation of Medtronic AVE S-670 coronary stent system. Whether the favorable results using the AVE GFX II can be translated to other stent types needs further evaluation.

Conclusions

Direct stenting is safe and feasible with high final success rate and low rate of complications. This technique is not compromized by the use of 6 French guides or the radial access, however, success rates are lower in more complex lesions, LCx lesions, and longer lesions. With miniaturized equipment and improved stent systems with lower profiles and better stent fixation, direct stenting can be attempted in most patients suitable for elective stentimplantation, resulting in a more efficient and probably safer treatment.

The long-term outcome is favorable with a low target lesion revascularization rate.

A randomized trial is needed for proper comparisons, especially concerning the angiographic restenosis rates.

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# Safety, efficacy and costs associated with direct coronary stenting compared to stenting after predilatation.

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## Abstract

Objectives Comparison of the in-hospital success rates, procedural costs and short-term clinical outcomes of direct stenting versus stenting after balloon predilatation.
Methods Four-hundred patients with angina pectoris and/or myocardial ischemia due to coronary stenoses in a single native vessel were randomized to either direct stenting versus stenting after predilatation. Baseline characteristics were evenly distributed between the two groups.
Results Procedural success rates were similar (96.0% direct stenting group vs. 94.5% predilatation) as well as final successful stent implantation (98.3% vs. 97.8%), while primary success rates of direct stenting alone was 88.3%, P=0.01. In multivariate analysis, angiographic lesion calcification was an independent predictor of unsuccessful direct stenting (odds ratio: 7.1, 95% confidence interval: 2.8-18.2, P<0.0001). Rates of troponin I rises >0.15 µg/L, used as a measure of distal embolization, were similar in both groups (17.8% vs. 17.1%). Rates of major adverse cardiac events at 30 days were 4.5% in the direct stenting group versus 5.5% in the predilated group (ns). Direct stenting was associated with savings in fluoroscopy time, angiographic contrast agent use, and a reduction in utilization of angioplasty balloons (0.4 vs. 1.17 balloons per patient; P<0.001). Mean per patient procedural costs associated with direct stenting versus predilatation were €2545±914 versus €2763±842 (P=0.01), despite the implantation of more stents in the directly stented group.
Conclusion Compared to a strategy of stenting preceded by balloon predilatation, direct stenting was equally safe and effective, with similar in-hospital and 30-day clinical outcomes, and modest procedural cost-savings. A calcified lesion predicted unsuccessful direct stenting.

## Introduction

When originally introduced, stents required predilatation of the stenotic lesion by an angioplasty balloon before being deployed.[1,2] However, technical advances in stent design and delivery systems now allow their direct implantation.[3] Direct stenting, defined as implantation of an intracoronary stent without prior balloon dilatation, is expected to reduce procedural time, fluoroscopy exposure, use of angiographic contrast agent, and consumption of various material, particularly angioplasty balloons, all converging to decrease procedural costs.[4-6] A potential disadvantage of this new approach is a limited visualization due to reduced distal run-off of contrast material through the undilated lesion, which may hamper positioning of the stent and proper choice of its dimensions. Other disadvantages may be incomplete stent deployment, stent loss and dislodgment at the lesion site or guide tip, distal embolization because of advancement of a stent through an undilated lesion, and failure to cross the lesion. This large, randomized, single-center trial of the Medtronic AVE S670 stent was conducted to compare the immediate and long-term outcomes after direct coronary stenting with those after stenting preceded by balloon dilatation. The hypotheses tested were that, compared to stenting after balloon predilatation, direct stenting is associated with similar or better in-hospital outcomes, and similar or decreased resources utilization and procedural costs.

## Methods

### Patient population

This study was approved by the Ethical Review Committee of the OLVG Hospital, and all study participants had signed a written informed consent form. Between January 1999 and June 2001, 400 eligible patients with stable or unstable angina pectoris and/or myocardial ischemia due to a non occlusive coronary stenosis of a single native vessel were enrolled. They were excluded from enrolment if they had a chronic total vessel occlusion, an ostial lesion, a lesion at a bifurcation, or a densely calcified lesion. Eligible patients were assigned 1:1 to either direct stenting or balloon predilatation by a computer-based randomization program.

### Stent implantation procedure

The interventional cardiology staff of OLVG includes 5 operators who adhered to the same study protocol. Aspirin, 500 mg, was administered before, and clopidogrel, 300 mg, was administered after the procedure to all patients. Heparin, 10.000 U, was given in an intravenous bolus at the beginning of the procedure, followed by additional hourly boluses of 5000 U. The use of glycoprotein IIb/IIIa receptor antagonists was left to the operators' discretion. The target lesion was accessed by standard techniques from the transradial, transfemoral, or transbrachial approach, and 6-French guiding catheters with appropriate curves were used. The target lesion was crossed with a 0.014-inch coronary

guidewire. When performing pre- or postdilatation, balloons of the shortest possible length were chosen to minimize the extent of vessel wall injury.
An AVE S670 stent (Medtronic Inc. Minneapolis, MN) was used in all procedures. It is mounted on a rapid exchange delivery balloon with maximal securement and a profile < 1 mm. Stents as short as possible were chosen to avoid unnecessary wall coverage, and sizes were selected to reach a stent/artery ratio of 1.1 to 1.2. The rated burst pressure of the delivery balloon is 16 atm. The Balloon pressure for final stent expansion was ≥ 14 atm. The use of additional postdilatation balloons was left to the operator's discretion, though not encouraged. The use of multiple stents was discouraged. Crossover from direct stenting to predilatation was permitted when the stent could not be advanced through the stenosis. In this case, standard balloon predilatation was performed, followed by further attempts to cross the lesion with the stent.
An optimal procedural result was defined as a residual stenosis < 30% of the luminal diameter by quantitative angiographic analysis (QCA).

### Post procedure drug regimen

Intravenous heparin was generally infused overnight a rate monitored by measurements of activated thromboplastin time, and discontinued on the day after the procedure. Clopidogrel, 75 mg/day was started on the day after the procedure, and continued for one month. Aspirin 100 mg/day was continued for at least six month.

### Quantitative coronary angiography

For each procedure, pre- and post stenting angiographic images were obtained in at least two reproducible orthogonal views, free of vessel overlapping and foreshortening, for computer-assisted QCA analyses. Intracoronary nitroglycerine, 100-300 μg, was injected before each angiographic recording, obtained before balloon dilatation, and/or immediately before and after stent implantation. During filming the catheter tip had to be empty of contrast agent, the patient in mid inspiration, and the table immobile. All angiograms were stored in a computer database and analyzed off-line, using the CAAS '99 Camtronics (Philips Medical System, Eindhoven, the Netherlands), and analyzed by an independent observer, according to an established protocol (Cardialysis, Rotterdam, the Netherlands). Regions of interest were chosen in the target vessel, and measurements of reference vessel diameter, minimal luminal diameter and percent diameter stenosis were made on end-diastolic frames. Lesion types were graded according to the American College of Cardiology/American Heart Association lesion characteristics classification.[7] Lesion length was measured as the distance between the proximal and the distal shoulder of the lesion, in mm. Tortuosity was defined as the presence of 2 or more bends > $45^0$ to the lesion.

### Endpoint definitions

Rate of procedural success was defined as 1) TIMI grade III flow,[8] 2) <30% residual in-stent % diameter stenosis, and 3) absence of major adverse cardiovascular events (MACE) during the index hospitalization. Procedural time was measured between the

time of sheath insertion and removal of the guiding catheter at the conclusion of the procedure. Fluoroscopy times were automatically recorded by the Poly Diagnost (C2) Digital Cardiac Imaging System (Philips). Additional endpoints included success of the intended treatment strategy, need for pre- and postdilatation, stent loss or dislodgment, occurrence of initial dissection after stent placement, and need for additional stents. In-hospital MACE was defined as death, Q-wave or non Q-wave myocardial infarction, acute vessel closure, target vessel revascularization, emergency coronary artery bypass graft surgery, and stroke. Diagnosis of a Q-wave myocardial infarction was based on prolonged typical chest pain and documentation of new pathological Q-waves (> 0.03 s) on electrocardiograms collected at baseline and before discharge from the hospital. Non-Q-wave infarction was defined as prolonged chest pain, associated with an increase in creatine kinase (CK) or its MB fraction (CK-MB) concentrations at least twice the upper limit of normal. Blood samples were collected at baseline and 6 h after the procedure. A rise in troponin I, CK and CK-MB was examined as a measure of embolization in both groups. A positive troponin rise was defined as: post procedure troponin minus baseline troponin concentration ≥ 0.15 µg/ L.
The incidence of hemorrhagic complications was also assessed.
Patients underwent clinical follow-up 30 days after the procedure. Angina class I to IV, and an electrocardiogram were recorded. Coronary angiography was only repeated for symptoms or signs consistent with the interim development of recurrent myocardial ischemia. MACE at one month included death, Q-wave or non Q-wave myocardial infarction, stent thrombosis, target vessel/lesion restenosis, repeat percutaneous revascularization of the target or non target vessel/lesion, target lesion revascularization, coronary artery bypass surgery and stroke. Revascularization of the target lesion was defined as the necessity for percutaneous or surgical revascularization performed for restenosis of the target lesion in association with recurrent angina, objective evidence of myocardial ischemia, or both. MACE at 30 days included events occurring during hospitalization.
The costs of the initial procedure were calculated per patient, and averaged for both groups. Procedural costs included those of the materials as well as costs of laboratory and staff time. The latter was calculated by multiplying the procedural time + 30 minutes by €17/ minute, based on unpublished, however time-tested cost estimate by Cardialysis. Materials included in the cost analysis were needles, sheaths, wires, guiding catheters, coronary guidewires, angioplasty balloons, premounted stents and angiographic contrast agent. The balloon of the stent delivery system was not included in the counts of balloons.

Statistical analysis
The primary analysis of angiographic, procedural and clinical outcome was based on the intention-to-treat principle. For comparison of continuous non-paired variables between the treatment groups, the unpaired two-tailed Student's t test was used or, in case of skewed data, the Mann-Whitney U-test. Comparison of categorical variables or composite clinical endpoints (any MACE) between the 2 groups was performed using

the Chi-square test. A paired t-test or Wilcoxon Rank test was used to detect changes in QCA measurements, and in blood levels of troponin I, CK and CK-MB. Spearman rank correlation testing (coefficient Rs) was performed to identify variables related to unsuccessful direct stent implantation. Among the variables identified, step-down logistic regression was performed until all remaining variables were significant, to reveal predictors of unsuccessful direct stent implantation. Continuous variables were expressed as mean±SD, and/or as percentages. Ninety-five percent confidence intervals (95% CI) were calculated for odds ratios. Statistical tests were carried out with the SPSS 10.0 statistical software package (Chicago, IL).

## Results

### Baseline demographics and lesion characteristics

Between January 1999 and June 2001, 400 eligible patients were randomized to either direct stenting (n=200 patients; 238 treated lesions) or to stenting preceded by balloon dilatation (n=200 patients; 231 lesions treated). The baseline demographic, clinical and lesion characteristics are listed in tables IA and IB. All characteristics were evenly distributed between the two treatment groups.

Table IA. Baseline demographic and clinical characteristics of patients treated with direct stenting (DS) versus stenting after balloon predilatation (PREDIL)

| Characteristic | DS (n=200) | PREDIL (n=200) |
|---|---|---|
| Age, y (mean±SD) | 61.0 ±10.9 | 60.4 ±11.4 |
| Men | 81.0 (162) | 80.5 (161) |
| CCS anginal class III/IV | 76.5 (153) | 76.5 (153) |
| Prior myocardial infarction | | |
| Q- wave | 14.5 (29) | 18.5 (37) |
| Non Q-wave | 19.0 (38) | 23.5 (47) |
| Prior percutaneous coronary intervention | 18.0 (36) | 12.5 (25) |
| Prior CABG | 5.5 (11) | 7.0 (14) |
| Triple vessel disease | 10.0 (20) | 10.0 (20) |
| Risk factors | | |
| Diabetes mellitus | 14.5 (29) | 16.5 (33) |
| Hypertension | 35.0 (70) | 35.0 (70) |
| Serum cholesterol ≥200 mg/dl | 61.0 (122) | 59.0 (118) |
| Family history of coronary artery disease | 50.0 (100) | 51.5 (103) |
| Peripheral vascular disease | 7.0 (14) | 9.5 (19) |
| Current smoking | 37.5 (75) | 36.0 (72) |

All values are % of patients (n) except where indicated otherwise.
CCS = Canadian Cardiovascular Society anginal class; CABG = Coronary artery bypass graft surgery

Table IB. Baseline coronary lesion characteristics of patients treated with direct stenting (DS) versus stenting after balloon predilatation (PREDIL)

| Lesion characteristic | DS (n=238 lesions) | PREDIL (n=231 lesions) |
|---|---|---|
| Location | | |
| Left anterior descending artery | 39.9 (95) | 40.7 (94) |
| Circumflex artery | 21.4 (51) | 26.0 (60) |
| Right Coronary Artery | 37.0 (88) | 30.7 (71) |
| Others | 1.7 (4) | 1.7 (4) |
| Class B2/C ¶ | 34.8 (83) | 31.6 (73) |
| Proximal tortuosity | 39.5 (94) | 34.2 (79) |
| Calcification | 12.2 (29) | 9.1 (21) |
| Thrombus | 4.6 (11) | 6.5 (15) |
| TIMI flow < III | 7.1 (17) | 8.7 (20) |

All values are % of lesions (n)

¶ According to the American College of Cardiology/ American Heart Association lesion characteristics classification, TIMI= Thrombolysis in Myocardial Infarction grade flow. .

Procedural and immediate angiographic results

The ultimately successful vascular access was via the radial approach in 86.5%, femoral in 9.5%, and brachial artery in 4% of the procedures. Table II summarizes the procedural results. Direct stenting was successful in 210 lesions (88.3%) significantly lower than the results of the intended treatment strategy in the predilated group (97.8%; P=0.01). In most unsuccessful cases of direct stenting attempts, the stent could not be advanced through the stenosis because of marked vessel tortuosity and/or densely calcified lesion. The baseline angiographic characteristics of the lesions that could not be directly stented differed from the lesions in which the attempt was successful. In unsuccessful attempts, lesions in the right coronary artery rank-correlated more prevalently (50% vs. 37%) as well as B2/C lesions (70% vs. 35%) and tortuosity (50% vs. 36%), while heavily calcified lesions were more common (46% vs. 12%) than in successful attempts. In multivariate analysis, among 16 demographic, clinical and angiographic variables tested, presence of calcification was an independent predictor of failure (odds ratio: 7.1, 95% CI 2.8-18.2, P<0.0001). Patient age, tortuosity, lesion location in the right coronary artery, and B2/C lesions were not independent predictors of failure, despite significant correlations on Spearman-rank analysis.

Nearly all lesions, which were not successfully stented directly, were successfully stented after predilatation, resulting in a final success rate of 97.9%. Two stents in the directly stented group were dislodged at the guide tip, one of which was successfully retrieved and the other lost. There was a trend towards a higher dissection rate after initial stent insertion in the directly stented group (P=0.06). Need for postdilatation was 9% higher after direct stenting than after predilatation (P=0.02). Postdilatation was prompted by undersizing of the stent in 19.3% of directly stented, versus 8.3% of predilated patients (P<0.001).

Table II. Procedural results in 238 directly stented (DS) versus 231 predilated (PREDIL) lesions, and 200 DS versus 200 PREDIL patients

| Results per lesion | DS (n=238) | PREDIL (n=231) | P |
|---|---|---|---|
| Stent length, mm (mean±SD) | 14.9±5.0 | 15.6±5.5 | 0.18 |
| Stent size, mm (mean±SD) | 3.0±0.4 | 3.0±0.4 | 0.83 |
| Success of intended treatment strategy | 88.3 (210) | 97.8 (226) | 0.01 |
| Need to predilate | 11.7 (28) | - | - |
| Dissection after initial stent placement | 8.8 (21) | 4.8 (11) | 0.06 |
| Stent for dissection | 6.3 (15) | 3.1 (11) | 0.15 |
| Post dilatation (overall) | 27.7 (66) | 18.6 (43) | 0.02 |
| Due to undersized stent | 19.3 (46) | 8.3 (19) | <0.001 |
| Due to suboptimal stent expansion | 8.4 (20) | 10.4 (24) | 0.53 |
| Results per patient | (n=200) | (n=200) | |
| Platelet GP IIb/IIIa antagonist usage | 5 (10) | 8 (15) | 0.41 |
| Ultimate procedural success | 96.0 (192) | 94.5 (189) | 0.31 |
| Procedural time, min (mean±SD) | 38.5±20.1 | 40.1±19.5 | 0.44 |
| Fluoroscopy time, min (mean±SD) | 10.1±7.8 | 10.3±8.2 | 0.80 |
| Use of contrast agent, ml (mean±SD) | 209±87 | 228±112 | 0.07 |

Results are presented as % (number of lesions or patients) unless stated otherwise.
GP=glycoprotein

Lesion length, determined by QCA, and stent length were similar in both groups (table II). The numbers of stents per lesion needed to cover the entire lesion length were also similar in the two groups, after exclusion of the stents used for the management of dissection. The overall average stent per lesion was < 1, as some lesions were ultimately not stented (direct stenting: 1.03±0.21 vs. predilatation: 0.99±0.30). While the immediate gain was highly significant in both groups (P<0.001), the magnitude of changes in reference vessel diameter, minimal lumen diameter, and diameter of stenosis were similar in both groups (table III). The ultimate procedural success rates, including the in-hospital MACE rate, were similar between the two treatment groups (96% with direct stenting vs. 94.5% with predilatation).

### In-hospital events

The in-hospital MACE rates were 3% in both treatment groups (table IV). One patient treated by direct stenting died during emergency coronary artery bypass surgery after an unsuccessful procedure complicated by a dissection of the left anterior descending artery. Autopsy revealed an acute anterolateral transmural myocardial infarction. Although there was no acute stent thrombosis in the directly stented group, a no re-flow phenomenon was observed in one patient after stent implantation, and a second patient suffered a distal vessel occlusion, and underwent further revascularization by emergency coronary bypass surgery. The four patients randomized to predilatation who developed transient acute vessel closure sustained a myocardial infarction. In one patient the stent occluded 4 h after the procedure. Vascular complications were limited to femoral hematomas or false aneurysms. No patient suffered a stroke.

Table III. Immediate angiographic results in 238 directly stented (DS) versus 231 predilated (PREDIL) lesions

| Pre-procedural characteristics | DS (n=238) | PREDIL (n=231) | P |
|---|---|---|---|
| Reference vessel diameter, mm | 2.87±0.61 | 2.84±0.60 | 0.30 |
| Lesion length (mm) | 9.1±3.6 | 9.3±4.6 | 0.72 |
| Minimal lumen diameter, mm | 0.99±0.33 | 1.00±0.30 | 0.68 |
| Percent diameter stenosis | 65.3±10 | 64.7±8 | 0.50 |
| Post-procedural characteristics | | | |
| Reference vessel, mm | 3.00±0.51 | 2.99±0.51 | 0.68 |
| Minimal lumen diameter, mm | 2.57±0.47 | 2.54±0.50 | 0.58 |
| Percent residual stenosis | 14.7±8.4 | 15.5±7.6 | 0.22 |
| Immediate gain* | | | |
| Reference vessel diameter, mm | 0.13±0.43 | 0.14±0.37 | 0.81 |
| Minimal lumen diameter, mm | 1.58±0.47 | 1.53±0.50 | 0.25 |
| Percent diameter stenosis | 50.1±12.0 | 49.1±12.3 | 0.15 |

Data are presented as mean±SD

*Immediate gain in reference vessel, minimal lumen diameter and percentage of stenosis within each group is highly significant (paired t-test: P< 0.001)

### Troponin and CK enzyme measurements

Mean troponin I rises > 0.15 µg/L between baseline and 6 h after the index procedure were of similar magnitude in both treatment groups (table V). Similarly, in a subgroup analysis of patients with unstable angina, no difference in magnitude of troponin rises was found between the direct stenting and the predilatation group. Increases in troponin I, CK and CK-MB concentrations were significant 6 h after the procedure in both groups (P<0.001), though the differences between the two treatment strategies were not significant.

### Clinical outcome at 30 days

At 30 days, MACE rates were 4.5% in directly stented patients versus 5.5% in the predilated group (table IV). No patient died after hospital discharge. Two directly stented patients suffered from subacute stent thromboses, resulting in one Q-wave and one non-Q-wave myocardial infarction. There were no significant differences between the two groups with respect to clinical endpoints. Relief of angina at 30 days in patients randomized to direct stenting (71.9%), versus predilatation (76.9%) was similar.

Table IV. In-hospital and cumulative 30 days major adverse cardiovascular events (MACE) in 200 patients who underwent direct stenting (DS), versus 200 patients who underwent stenting preceded by balloon dilatation (PREDIL)

| EVENTS* | DS % (n) | PREDIl % (n) |
|---|---|---|
| In-hospital | N=200 | N=200 |
| Death | 0.5 (1) | 0 |
| Acute Vessel Closure | 1.0 (2) | 2.0 (4) |
| Myocardial infarction | | |
| Q-wave | 0 | 0.5 (1) |
| non-Q-wave | 1.5 (3) | 2.0 (4) |
| Target vessel revascularization | 0.5 (1) | 1.0 (2) |
| Emergency CABG | 1.5 (3) | 1.5 (3) |
| OVERALL IN-HOSPITAL MACE | 3.0 (6) | 3.0 (6) |
| 30 DAYS | N=200 | N=200 |
| Death | 0.5 (1) | 0 |
| Stent thrombosis | 1.0 (2) | 0.5 (1) |
| Myocardial infarction | | |
| Q-wave | 0.5 (1) | 0.5 (1) |
| non-Q-wave | 2.0 (4) | 2.5 (5) |
| Target lesion revascularization | 1.5 (3) | 1.0 (2) |
| CABG | 3.0 (6) | 1.5 (3) |
| Further PCI** | 2.0 (4) | 2.0 (4) |
| CUMULATIVE 30-DAY MACE | 4.5 (9) | 5.5 (11) |

Results indicate percentages (numbers) of patients and are rank-ordered

* Clinical endpoints and MACE did not differ significantly between the 2 groups (P>0.2).

** Includes further target and non-target vessel/lesion PCI.

CABG = Coronary artery bypass grafting; PCI = Percutaneous coronary intervention.

Table V. Rise in postprocedural blood troponin I, creatine kinase (CK) and CK-MB concentrations 6 hours after direct stenting (DS) versus predilatation (PREDIL)

| | DS | PREDIL | P |
|---|---|---|---|
| Troponin I rise, µg/L | 0.19 (0-6.30) * | 0.24 (0-16.7) * | 0.75 |
| Troponin I rise >0.15 µg/L (% of patients) | 17.8 | 17.1 | 0.88 |
| Stable angina | 17.1 | 14.3 | 0.60 |
| Unstable angina | 19.6 | 22.4 | 0.82 |
| CK rise, U/L | 14.4 (0-669.0) * | 13.7 (0-265.0) * | 0.55 |
| CK-MB rise, U/L | 2.3 (0-25.0) * | 1.9 (0-24.0) * | 0.55 |

Results are mean values (range) unless specified otherwise.

*Rises in troponin I, CK and CK-MB were significant in both groups (P<0.001, Wilcoxon rank test).

Upper normal values: CK = 190 U/L, CK=MB =16 U/ L, Troponin I = 0.05 µg/L.

Procedural costs and resources utilization
Mean duration of procedures and of radiation exposure did not differ significantly between the treatment groups. A trend was observed toward a greater amount of angiographic contrast agent used in the predilated group (19 ml/patient; P=0.07). There was a significant difference in favor of direct stenting in the amount of balloons used per patient (direct stenting: 0.4 ±0.73 vs. predilatation: 1.17 ±0.54; P< 0.001). On the other hand more stents per patient were used in the directly stented group (1.33 ±0.59 vs. 1.18 ±0.60; P=0.01). Overall consumption of needles, sheaths, wires, guiding catheters and coronary guide wires was the same in both groups. Procedural costs per patient were significantly, albeit modestly, lower in the direct stenting than in the predilated group (€2545±914 vs. €2763±842; P=0.01), representing a mean saving of €218 per patient (figure 1).

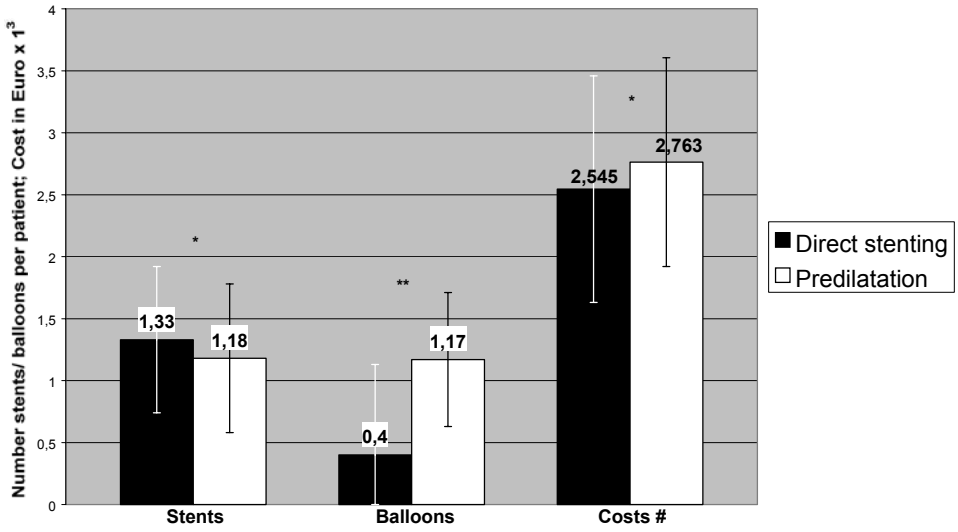


Figure 1. The significant reduction in the use of angioplasty balloons resulted in a modest but significantly lower procedural costs with direct stenting than with balloon predilatation.
Data represent costs per patient averaged (±SD) in each group. P<0.05, ** P<0.001

## Discussion

The main finding of this randomized study was an equal overall safety and effectiveness of direct stenting compared to stenting after predilatation in this patient population, with the occurrence of few procedural complications, similar in-hospital and 30-day outcomes, and modest cost-savings. As expected the success rate of the intended treatment strategy was higher in patients randomized to predilatation. However the

ultimate procedural success rates of the two methods were similar, and equivalent to other randomized studies of direct stenting.[9,10] The involvement of less experienced trainees in some of the procedures may explain the relatively high crossover rate of 11.7%. The unexpanded stent was successfully removed through the guiding catheter in nearly all cases. From the subgroup analysis, failure of direct stenting in this study was concentrated mainly among patients with mildly calcified lesions, while also disease of the right coronary artery, B2/C lesions, and tortuous lesions were more common in this subgroup. In addition, in multivariate analysis a mildly, angiographically determined, calcified lesion was a predictor of unsuccessful direct stenting. Although previously reported by others[3,6,9], age, and lesion complexity were not retained in our multivariate analysis, probably superseded by calcification. This suggests that age per se is not a contraindication to direct stenting, provided the lesion is not calcified.

A hypothetical benefit of direct stenting may be a lower risk of dissection by immediate sealing of new dissection planes. However, in this study, a trend was observed toward a higher rate of dissection after initial stent placement in the directly stented lesions. The dissection rate of 8.8% after direct stenting in this study was high compared to 0 to 7% reported previously by others, although, in these studies, the types of dissections counted were not precisely described.[6,9,11-16] In our study, all dissections occurring after initial stent placement, from type A to F, were counted.

It is believed that, because of the poor run-off of angiographic contrast material distal to the lesion associated with direct stenting, positioning of the stent may be less precise, perhaps resulting in the use of stents longer than necessary, to guarantee the coverage of the entire lesion, causing injury to healthy segments of the vessel wall. We did not confirm this hypothetical adverse effect of direct stenting. The rates of stent length overseeing in the direct stenting (1: 1.64 mm) and predilatation (1: 1.67 mm) groups were not different, lesion length and stent length being also similar between the two groups. In addition, the mean number of stents needed to cover the lesions was similar between the study groups. Thus, direct stenting did not lead to longer stents, and overseeing of the stent diameter did not occur.

Postdilatation because of undersizing of the stent was more frequently observed after direct stenting. Since the subjective estimate "undersizing for postdilatation" was determined by the operator, and stent length and diameter were accurately chosen according to the lesion length and reference diameter measured, postdilatation may have been unnecessarily performed in the direct stented group. An explanation may be uncertainty of the operator when having to perform the more challenging technique of direct stenting.

Incomplete stent expansion in non predilated lesions, a potential limitation of direct stenting, was not observed in this study, as stent and lesion diameters were similar, and postdilatation because of suboptimal stent expansion was performed equally, in both groups.

A noteworthy finding was the modest acute gain in reference vessel measured in both groups. This may have been due to a cumulative effect of the administration of multiple nitroglycerine doses after baseline angiography, and/or a flow-induced vasodilatation.

This phenomenon has been observed in other studies, though its precise mechanism remains unclear.
Procedural and fluoroscopy times did not differ between the study groups and were long compared to other studies.[4,5,10] In a large randomized trial, procedural duration and fluoroscopy time were modestly reduced by direct stenting[10]. After exclusion of the procedures in which trainees participated actively, procedural and fluoroscopy times associated with direct stenting versus predilatation were 30.5±15.5 and 31.1±14.4 min and 7.1±4.6 minutes and 7.8±6.1, respectively.
As expected fewer balloons were used in the directly stented group, resulting in a modest cost saving. In-hospital events were not included in the cost-analysis, since the MACE rates associated with the two strategies were equivalent. Several other studies have also found a cost reduction in favor of direct stenting.[4,5,9] Likewise, the absence of effect of direct stenting on in-hospital and 30-day MACE rates is concordant with results of other randomized studies comparing the two strategies. [4,5,9,10,12,13]
There was no evidence that distal embolization caused by the advancement of a stent through an undilated lesion was a disadvantage of direct stenting, since the rise in troponin I, used as a sign of distal embolization, was similar in both treatment groups. The postprocedural rise in CK, CK-MB enzymes and troponin I was significant in both groups, consistent with mild myocardial injury caused by the intervention.
With improving stent designs and the high final success rate after predilatation in failed direct stent cases, it is possible to attempt direct stenting in many cases.

Limitations of the study
The selection of lesions included in this study was mostly based on the operators' experience, who judged their suitability for both treatment strategies. The absence of strict exclusion criteria, for example calcification, and the active participation of trainees in the procedure may have negated some of the benefits of direct stenting. In addition, these data reflect the performance of a single institution. However, this results in more uniformity to the study.
In conclusion, in this study, direct stenting was safe and effective in the treatment of single coronary artery lesions, with ultimate procedural success rates equivalent to stenting preceded by balloon dilatation. Direct stenting did not lead to the use of longer stents, and it was not associated with fewer dissections or distal embolizations. Angiographic lesion calcification was a predictor of failure of direct stenting. Although direct stenting was highly successful, its performance yielded only a modest cost saving compared with predilatation followed by stent placement.

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# Direct coronary stent implantation does not reduce the incidence of in-stent restenosis or major adverse cardiac events: six month results of a randomized trial

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## Abstract

Study objectives: To compare long-term angiographic, clinical and economic outcome of direct stenting versus stenting after balloon predilatation.
Patient population and methods: Four-hundred patients with coronary stenoses in a single native vessel were randomized to direct stenting versus stenting after predilatation. Major adverse cardiac and cerebral event (MACCE) was defined as the combination of death, myocardial infarction, stent thrombosis, target restenosis, repeat target- and non-target-vessel-related percutaneous coronary intervention, target lesion revascularization, coronary artery bypass surgery and stroke.
Results: Stents were successfully implanted in 98.3% of patients randomized to direct stenting versus 97.8% randomized to stenting preceded by predilatation. The primary success rate of direct stenting was 88.3%, versus 97.8% for stenting preceded by balloon dilatation (P=0.01). The angiographic follow-up at six months included 333 of the 400 patients (83%). The binary in-stent restenosis rate was 23.1% of 163 patients randomized to direct stenting versus 18.8% of 166 patients randomized to balloon predilatation (P=0.32). At 185±25 days, MACCE had occurred in 31 of 200 (15.5%) patients randomized to direct stenting, versus 33 of 200 (16.5%) randomized to predilatation (P=0.89). At 6 months, costs associated with the direct stenting strategy (Euros 3,222/patient) were similar to those associated with predilatation (Euros 3,428/patient, P=0.43). However, procedural costs were significantly lower.
It is noteworthy that, on multivariate analysis, a baseline C-reactive protein level > 10mg/L was a predictor of restenosis (odds ratio: 2.10, P=0.025) as well as of MACCE (odds ratio: 1.94, P=0.045).
Conclusions: Compared to stenting preceded by balloon predilatation, direct stenting was associated with similar 6-month restenosis and MACCE rates. Procedural, but not overall 6-month costs, were reduced by direct stenting. An increased baseline CRP level was an independent predictor of adverse long-term outcome after coronary stent implantation.

## Introduction

Direct coronary stent implantation, defined as stenting without prior balloon dilatation, is a new treatment strategy for coronary artery disease, enabled by the development of advanced stent designs, and of delivery systems with lower crossing profiles, high securement and higher burst pressure ratings. [1-11] Recent studies of direct stenting have confirmed its feasibility and safety, and its likelihood to shorten revascularization procedures and reduce the consumption of medical resources, thus increasing cost-effectiveness. [1,3,6,9,11-17] In addition, results in rabbits have suggested for iliac artery that direct stenting is associated with less vessel wall damage and endothelial denudation from fewer balloon inflations, and stimulation of the process of reendothelialization, resulting in attenuated neointimal proliferation. [18] However, few studies have examined the putative long-term advantages of direct stenting with respect to clinical and angiographic restenosis and cost-effectiveness. The purpose of this randomized study was to compare the angiographic, clinical and economic outcomes of direct stenting with stenting after balloon predilatation up to six months after the index procedure.

### Patient population and methods

The Ethical Review Committee of the OLVG Hospital approved this study, and all participants had signed a written informed consent form. Between January 1999 and June 2001, 400 eligible patients with stable or unstable angina pectoris, and/or myocardial ischemia due to a non-occlusive coronary stenosis of a single native vessel stentable and technically feasible for direct stenting were enrolled. Patients with complete chronic vessel occlusions, or ostial, bifurcation, or densely calcified lesions, or lesion length > 30mm, diameter > 2.5mm were not included in the study. Eligible patients were assigned 1:1 to either direct stenting or balloon predilatation using a computer-based randomization program.

### Stent implantation procedure

The interventional cardiology staff of OLVG includes 5 operators who adhered to the same study protocol. Aspirin, 500 mg, was administered before, and clopidogrel, 300 mg, was administered after the procedure to all patients. Heparin, 10.000 U, was given in an intravenous bolus at the beginning of the procedure, followed by additional hourly boluses of 5000 U. The use of glycoprotein IIb/IIIa receptor antagonists was left to the operators' discretion. The target lesion was accessed by standard techniques from the transradial, transfemoral, or transbrachial approach, and 6-F guiding catheters with appropriate curves were used. The target lesion was crossed with a 0.014-inch coronary guidewire. When performing pre- or postdilatation, balloons of the shortest possible length were chosen to minimize the extent of vessel wall injury.
An AVE S670 stent (Medtronic Inc. Minneapolis, MN) mounted on a rapid exchange delivery balloon with maximal securement and a < 1 mm profile was used in all procedures. Stents as short as possible were chosen to avoid unnecessary wall coverage,

and sizes were selected to reach a 1.1 to 1.2 stent/artery ratio. The burst pressure rating of the delivery balloon is 16 atm. The balloon pressure for final stent expansion was ≥ 14 atm. The use of additional postdilatation balloons was left to the operator's discretion, though not encouraged, and the implantation of multiple stents was discouraged. Crossover from direct stenting to predilatation was permitted when the stent could not be advanced through the stenosis. In such cases, standard balloon predilatation was performed, followed by further attempts to cross the lesion with the stent.
An optimal procedural result was defined as a residual stenosis < 30% of the luminal diameter on online quantitative angiographic analysis (QCA) in the catheter laboratory.

Post procedure drug regimen
Intravenous heparin was generally infused overnight at a rate based on measurements of activated thromboplastin time, and was discontinued on the day after the procedure. Clopidogrel, 75 mg/day, was started on the day after the procedure, and continued for one month. Aspirin, 100 mg/day, was administered on the day after the procedure and continued for ≥ six month.

Quantitative coronary angiography
At each procedure, pre- and post-stenting angiographic images were obtained in at least two reproducible orthogonal views, free of vessel overlapping and foreshortening, for computer-assisted QCA analysis. Intracoronary nitroglycerine, 100-300 μg, was injected before each cineangiographic recording, which were made before balloon dilatation, and/or immediately before and after stent implantation. During filming, the catheter tip had to be empty of contrast agent, the patient in mid inspiration, and the table immobile. All angiograms were stored in a computer database and analyzed off-line, using the CAAS '99 Camtronics (Philips Medical System, Eindhoven, the Netherlands), and analyzed by an independent observer, according to an established protocol (Cardialysis, Rotterdam, the Netherlands). Regions of interest were chosen in the target vessel, and measurements of reference vessel diameter, minimal luminal diameter (MLD) and percent diameter stenosis (%DS) were made on end-diastolic frames. Lesion types were graded according to the American College of Cardiology/American Heart Association lesion characteristics classification. Lesion length, in mm, was measured as the distance between proximal and distal shoulders of the lesion. Tortuosity was defined as the presence of 2 or more bends > $45^0$ proximal to the lesion.
Binary restenosis was defined as a luminal narrowing ≥ 50% at 6 months. MLD and %DS were measured within the stent's edges. Plaque volumes of target segments before and after the procedure and at six month were measured by computer-assisted quantitative coronary angiography. All unscheduled angiograms prompted by return of symptoms, abnormal stress testing, or other untoward coronary events, were also analyzed.

End point definitions

The primary endpoint of this study was to compare, up to six months, the composite incidence of major adverse cardiac and cerebral events (MACCE) in both groups. MACCE was defined as death from all causes, Q- and non-Q-wave myocardial infarction, stent thrombosis, target restenosis, repeat target- and non-target-vessel-related percutaneous coronary intervention (PCI), target lesion revascularization (TLR), coronary artery bypass graft (CABG) and stroke. Revascularization of the target lesion was defined as PCI or CABG performed for restenosis of the target lesion in association with recurrent angina, objective evidence of myocardial ischemia or both. Procedural success was defined as TIMI grade III flow [20], < 30% final, residual in-stent %DS, and absence of MACCE during the index hospitalization. Diagnosis of a Q-wave myocardial infarction was based on prolonged typical chest pain and documentation of new, > 0.03 sec Q-waves on standard electrocardiogram, recorded at baseline and before discharge of the patient from the hospital. Non-Q-wave infarction was defined as a blood creatine kinase, or its MB fraction, > twice the upper limit of normal with or without prolonged chest pain.

Additional endpoints were the comparison between the two groups of success of the intended treatment strategy, final successful stent placement, procedural success rates, recurrent Canadian Cardiovascular Society (CCS) class III and IV angina pectoris and medical costs. [19] The 6-month angiographic endpoints were in-stent binary restenosis and plaque volume of target lesion segment.

Patient follow-up

At 30 days patients visited the outpatient department for assessment of their CCS anginal status, and recording of interim MACCE, coronary intervention, or clinical manifestations consistent with recurrent myocardial ischemia. They also underwent follow up angiography for QCA at six months. The 6-month angiograms were waived in patients who had undergone an earlier clinically-indicated angiographic examination in which in-stent restenosis was detected. A 12-lead electrocardiogram was systematically recorded at each clinical visit, and other non-invasive tests as necessary.

Medical costs and effectiveness

The balance between costs and effects was evaluated immediately after the procedure, and at six months. The costs of the initial procedure were calculated per patient, and averaged in both groups. Procedural costs included the materials and laboratory and staff time. Laboratory and staff time were calculated by multiplying the procedural time + 30 min by Euros 17/min; the latter figure was based on time-tested cost estimates, obtained from a large data set collected by a company linked to the university hospital of Rotterdam, the Netherlands (data unpublished). Materials included in the cost analysis were needles, sheaths, wires, guiding catheters, coronary guidewires, angioplasty balloons, premounted stents and angiographic contrast agent. The balloon of the stent delivery system was not included in the overall count of balloons. Procedural effectiveness was expressed as the attainment of a postprocedural < 30 % DS of all

lesions treated. Six-month costs were estimated by multiplying adverse clinical events by pre-estimated event costs (repeat PCI = Euros 4000, CABG= Euros 12000, Q-wave MI= Euros 3000). Effectiveness at six months was defined as an MACCE-free status.

### Statistical analysis

With a two-sided significance level set at 0.05 and an 80% power, it can be shown that the sample size of 400 patients will allow to detect a minimum proportional treatment difference (MACCE) of 8% at 180 days. The primary analysis of angiographic, procedural and clinical outcomes was based on the intention-to-treat principle. For comparison of continuous non-paired variables between the treatment groups, the unpaired two-tailed Student's t-test was used or, in case of skewed data, the Mann-Whitney U-test. Comparison of categorical variables or composite clinical endpoints (any MACCE) between the 2 groups was performed using the Chi-square test. Event-free Kaplan-Meier curves were based on the absence of MACCE. Differences in survival time were assessed by the log-rank test. As events continued to occur 30 days after the six-month follow-up, patients were censored at 210 days. A paired t-test or Wilcoxon Rank test was used to determine a potential gain or loss in mean luminal diameter. Spearman rank correlation testing (coefficient Rs) was performed to identify variables related to MACCE at six months and to binary restenosis. Logistic regression analysis was performed among these variables to detect predictors of MACCE and restenosis. [21] Continuous variables were expressed as mean ± standard deviation (SD) and/or as a percentage. Ninety-five percent confidence intervals (95% CI) were calculated for odds ratios. Statistical tests were carried out with the SPSS 10.0 statistical software package (Chicago, IL).

## Results

### Baseline demographics and lesion characteristics

In the 200 patients randomized to direct stenting, 238 lesions were treated, versus 231 lesions in the 200 patients randomized to predilatation. All baseline demographic, clinical and lesion characteristics were evenly distributed between the two treatment groups (table 1).

### Safety and efficacy

The ultimately successful vascular access was via the radial approach in 86.5%, femoral in 9.5%, and brachial artery in 4% of the procedures. Direct stenting was successful in 210 lesions (88.3%), a significantly lower percentage than the primary success of stenting preceded by balloon dilatation (97.8%; P=0.01). In most unsuccessful direct stenting attempts, the stent could not be advanced through the stenosis because of marked vessel tortuosity and/or a densely calcified lesion. Nearly all lesions unsuccessfully stented directly, were successfully stented after predilatation, for a final success rate of 97.9%.

Table 1. Baseline characteristics of patients randomized to direct stenting (DIRECT) versus predilatation followed by stent placement (PREDIL)

| CHARACTERISTICS | DIRECT (n=200) | PREDIL (n=200) |
|---|---|---|
| Age, years (mean±SD) | 61.0±10.9 | 60.4±11.4 |
| Men/Women | 81/19 | 81/19 |
| Diabetics/smoking/hypertension/hypercholesterolemia | 15/38/35/61 | 17/36/35/59 |
| Prior MI/PCI/CABG | 34/18/6 | 42/13/7 |
| Anginal CCS classes I/II/III/IV | 6/18/47/29 | 4/20/40/36 |
| Number of diseased coronary arteries (1/2/3) | 67/23/10 | 69/21/10 |
| Use of glycoprotein IIb/IIIa inhibitor | 5 | 8 |
| Elevated preprocedural CRP level (>10 mg/L) | 21 | 19 |
| Lesion numbers | 238 | 231 |
| Lesion location | | |
| Left Anterior Descending artery | 41 | 41 |
| Circumflex Artery | 22 | 28 |
| Right Coronary Artery | 37 | 31 |
| ACC/AHA lesion classification type A/B1/B2/C | 27/38/24/11 | 21/47/23/9 |
| TIMI grade flow 0/I/II/III | 1/2/5/92 | 0/4/4/92 |
| Lesion length, mm (mean±SD) | 9.1±3.6 | 9.3±4.6 |

Unless indicated otherwise, all values represent % of patients or lesions per treatment group.
MI = Myocardial Infarction, PCI = Percutaneous Coronary Intervention, CABG = Coronary Artery Bypass Grafting, CCS = Canadian Cardiovascular Society, CRP = C-reactive protein, ACC/AHA = American College of Cardiology/ American Heart Association, TIMI = Thrombolysis in Myocardial Infarction.

The ultimate procedural success rates, including the in-hospital MACCE rate, were 96% with direct stenting versus 94.5% with predilatation (ns). One patient treated by direct stenting died during emergency CABG after an unsuccessful procedure complicated by dissection of the left anterior descending coronary artery. Autopsy confirmed the presence of an acute anterolateral transmural myocardial infarction. Although no acute stent thrombosis occurred in the directly stented group, the no-reflow phenomenon was observed in one patient after stent implantation, and a second patient, who suffered a distal vessel occlusion, had to undergo further revascularization by emergency CABG. Four patients randomized to predilatation developed transient vessel closure complicated by myocardial infarction. In one patient, stent occlusion occurred 4 h after the procedure. Vascular complications were limited to femoral haematomas or false aneurysms. No patient suffered a stroke while in hospital.

### Angiographic outcome and restenosis

Follow-up angiography was performed at six months in 333 patients (83%). Causes of missing follow-up angiograms included death (n=3), and patient refusal (n=64). Baseline, immediately postprocedural and 6-month angiographic measurements are listed in table 2. Figure 1 presents the cumulative distributions of acute gain, late loss and net gain for the two treatment strategies. At six months, the angiographic binary in-stent restenosis rates in 163 overall direct stenting attempts, 146 successful direct stenting attempts, and in 166 patients randomized to predilatation were 23.1%, 21.9% and 18.8%, respectively (ns).

Table 2. Immediate and 6-month quantitative coronary angiographic measurements in patients randomized to direct stenting (DIRECT) versus stenting preceded by predilatation (PREDIL)

| MEASUREMENT<br>ANGIOGRAPHIC FEATURES | DIRECT (n=238) | PREDIL (n=231) | P |
|---|---|---|---|
| Reference vessel diameter, mm | | | |
| Baseline | 2.87±0.61 | 2.84±0.60 | 0.30 |
| After Procedure | 3.00±0.51 | 2.99±0.51 | 0.68 |
| Six-month follow-up | 3.23±0.69 | 3.14±0.61 | 0.21 |
| Minimal lumen diameter, mm | | | |
| Baseline | 0.99±0.33 | 1.00±0.30 | 0.68 |
| After Procedure | 2.57±0.47 | 2.54±0.50 | 0.58 |
| Six-month follow-up | 2.02±0.65 | 2.02±0.68 | 0.93 |
| Percent diameter stenosis, % | | | |
| Baseline | 65.3±10 | 64.7±8 | 0.50 |
| After Procedure | 14.7±8 | 15.5±8 | 0.22 |
| Six-month follow-up | 37.1±16 | 36.2±16 | 0.54 |
| Plaque volume, mm3 | | | |
| Baseline | 28.4±21.0 | 28.6±22.2 | 0.89 |
| After Procedure | 5.0±8.6 | 5.1±6.5 | 0.84 |
| Six-month follow-up | 29.1±28.3 | 23.0±22.3 | 0.02 |
| Acute gain, mm* | 1.58±0.47 | 1.53±0.50 | 0.25 |
| Late loss, mm | 0.61±0.54 | 0.58±0.48 | 0.57 |
| Net gain, mm | 1.0±0.62 | 1.0±0.62 | 0.57 |
| Binary restenosis rate, % | 23.1 | 18.8 | 0.32 |

Except for binary restenosis rate, values are mean ± standard deviation. P values reflect comparisons between DIRECT and PREDIL.

*Acute gain in minimal lumen diameter in each group was highly significant (paired t-test: P<0.001)

Mean plaque volume at six months had returned to its baseline value in the direct stenting group, whereas it remained significantly lower in patients who had undergone stenting after predilatation (23.0 ± 22.3 $mm^3$ vs. 28.6 ± 22.2 $mm^3$, P=0.02), despite equivalent mean minimal luminal diameters and percent diameter stenoses. At six months, the mean reference vessel diameter was significantly greater than at baseline in the overall study population (p<0.001 for both groups pooled), though not different between the two study groups.

## One-month and late clinical outcomes

The 1-month and late clinical outcomes are presented in table 3. The 30-day MACCE rates were 4.5% and 5.5% in patients randomized to direct stenting and predilatation, respectively. No patient died after discharge from the hospital. Two patients in the direct stenting group developed subacute stent thrombosis complicated by one Q-wave and one non-Q-wave myocardial infarction, respectively. There were no significant between-groups differences in clinical endpoints. The 30-day angina-free statuses were 71.9% in patients randomized to direct stenting versus 76.9% in patients randomized to predilatation (ns).

Table 3. Cumulative incidence of MACCE at one and six months in direct stenting (DIRECT, n=200) and predilatation (PREDIL, n=200) study groups

| ADVERSE EVENT | DIRECT % (n) | PREDIL% (n) |
|---|---|---|
| ONE MONTH | | |
| Death | 0.5 (1) | 0 |
| Stent thrombosis | 1.0 (2) | 0.5 (1) |
| Myocardial infarction | | |
| Q-wave | 0.5 (1) | 0.5 (1) |
| non Q-wave | 2.0 (4) | 2.5 (5) |
| Target lesion revascularization | 1.5 (3) | 1.0 (2) |
| CABG | 3.0 (6) | 1.5 (3) |
| Repeat PCI* | 2.0 (4) | 2.0 (4) |
| Stroke | 0 | 0 |
| 1-MONTH MACCE | 4.5 (9) | 5.5 (11) |
| | | |
| SIX MONTHS | | |
| Follow up duration, days (mean ±SD) | 186 ±26 | 184 ±24 |
| MACCE | | |
| Death due to coronary event | 0.5 (1) | 0 |
| Death due to carcinoma/undetermined | 1.0 (2) | 0 |
| Myocardial infarction | | |
| Q-wave | 1.0 (2) | 1.0 (2) |
| non Q-wave | 2.0 (4) | 3.0 (6) |
| Target lesion revascularization | 6.5 (13) | 7.5 (15) |
| CABG | 4.0 (8) | 3.0 (6) |
| Repeat PCI | 11.0 (22) | 12.5 (25) |
| Stroke | 0.5 (1) | 0 |
| OVERALL LATE MACCE | 15.5 (31) | 16.5 (33) |
| OTHERS | | |
| Anginal CCS classes I/II/III/IV | 80.6/13.3/5.1/1.0 | 80.8/11.1/6.1/2.0 |
| Exercise test (+/-/±/ND) | 6.3/71.4/6.9/15.3 | 4.2/71.4/8.5/15.9 |

Except for duration of follow up, values represent percent of patients (number of patients)
*Includes target and non-target repeat PCI.
CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention; CCS = Canadian Cardiovascular Society; Exercise test (+/-/±/ND) = positive/negative/equivocal/not done.

At the end of a mean observation period of 185 ±25 days, MACCE had occurred between study enrolment and the end of follow-up in 31 of 200 patients (15.5%) randomized to direct stenting, versus 33 of 200 patients (16.5%) randomized to predilatation (P=0.89). Cardiac arrest was presumed for the single patient in the direct stenting group, whose cause of death had not been precisely determined. Kaplan-Meier event-free survival curves (figure 2) for patients randomized to direct stenting and predilatation were similar (P=0.96; log-rank test).

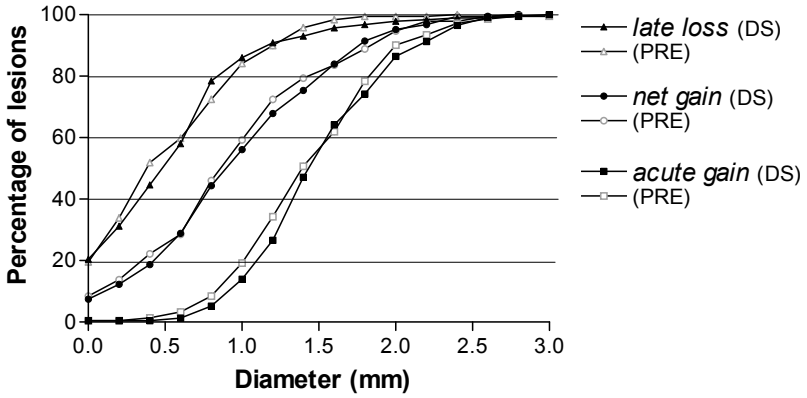


Figure 1. Cumulative distribution of late loss, net gain and acute gain in minimal lumen diameter (MLD). Direct stenting (DS) vs. stenting after predilatation (PRE). Late loss = MLD after stenting minus MLD at follow-up. Net gain = MLD at follow-up minus MLD at baseline. Acute gain = MLD after stenting minus MLD at baseline.

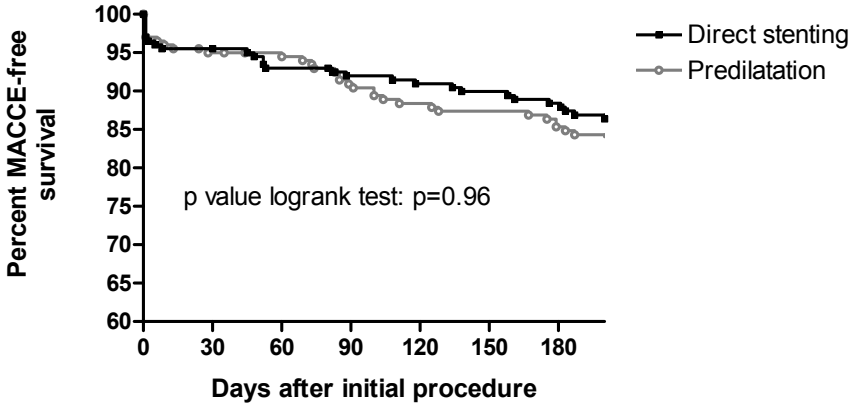


Figure 2. Kaplan-Meier survival free from MACCE up to 210 days after the index procedure in each study group.

Multivariate analysis

Among 31 demographic, clinical and angiographic variables tested, diabetes mellitus (odds ratio: 2.35, 95% CI: 1.2-4.6, P=0.014), a smaller MLD after stenting as expressed in millimeter (odds ratio: 2.86, 95% CI: 1.5-5.4, P=0.001) and a C-reactive protein concentration > 10 mg/L (odds ratio: 2.10, 95% CI: 1.1-4.0, P=0.025) were independent predictors of restenosis (figure 3). The relation between MLD after stenting divided in subgroups and the binary restenosis rate is illustrated in figure 4.

Figure 3 also shows that diabetes mellitus (odds ratio: 2.22, 95% CI: 1.1-4.4, P=0.024), triple vessel coronary disease (odds ratio: 2.27, 95% CI: 1.0-5.1, P=0.049), baseline CRP concentration >10 mg/L (odds ratio: 1.94, 95% CI: 1.0-3.7, P=0.045), left anterior

descending (odds ratio: 4.29, 95% CI: 1.9-9.6, P<0.001) and left circumflex (odds ratio: 4.46, 95% CI: 1.9-10.5, P<0.001) coronary arteries as target vessels, were independent predictors of cumulative MACCE up to six months.
A high baseline CRP also predicted an adverse outcome at one month (odds ratio: 4.20, P=0.046). Baseline CRP, expressed as a continuous variable, was not retained in our model, although it was separately associated with MACCE (Rs = 0.15, P=0.012).

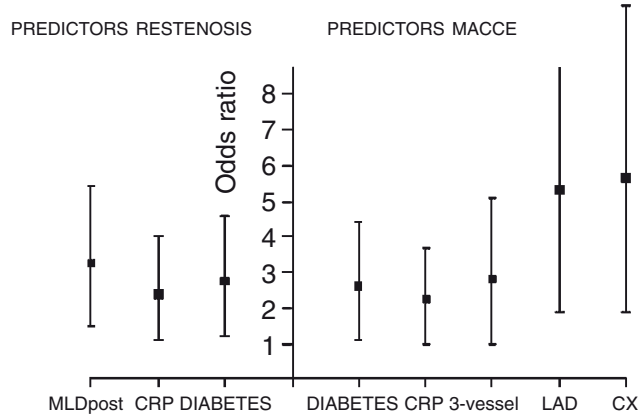


Figure 3. Independent predictors (odds ratios; 95% CI) of in-stent restenosis (left panel) and six-month cumulative MACCE (right panel)
MLDpost = minimal lumen diameter after stenting (mm); CRP = C-reactive protein concentration > 10mg/dL; 3-vessel = presence of triple vessel coronary artery disease; LAD = lesion located in left anterior descending coronary artery; CX = lesion located in left circumflex coronary artery.

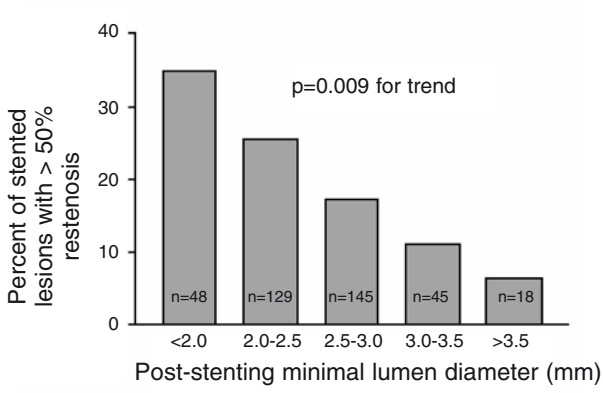


Figure 4. Relationship between minimal lumen diameter after stenting and binary 6-month in-stent restenosis. N = number of lesions.

Costs and effectiveness
Direct stenting was associated with a reduced consumption of angioplasty balloons (0.4 vs. 1.17 balloons/patient, p<0.001), thus, lower procedural costs (Euros 2,545±914 vs. 2,763±842, ΔC=-218, P=0.01), than with predilatation. There were no significant differences in overall costs after 6 months, owing probably to the wide variability of follow-up costs (Euros 3,222±2,713 vs. 3,428±2,466, ΔC=-206, P=0.43). Efficacy at one (ΔE=0.5%) and six months (ΔE=1.0%) was the same in both treatment groups.

## Discussion

Technical progress made in the past 10 years in stents design and in their delivery systems has eliminated the need for angioplasty balloons to predilate coronary lesions before stent implantation. This controlled trial examined the long-term angiographic, clinical and economic outcomes of this new strategy, known as direct stenting.
A primary implantation success rate of 88.3% was achieved with direct stenting. The final procedural success rate, including 10% of patients in whom balloon predilatation was ultimately needed, was 96%, similar to the success rate observed in the group randomized to stenting after predilatation, and equivalent to that typically observed with standard methods in this type of patient population. Against our expectations based on results of animal studies, there seemed to be no long-term angiographic or clinical advantage conferred by direct stenting in this group of patients. Direct stenting did not reduce the incidence of binary restenosis, and mean plaque volume at six months was, in fact, higher in the directly stented lesions. The lower rate of restenosis observed in directly stented animals does not seem to be extrapolated to humans.
Early and long-term MACCE rates were comparably low, confirming that a systematic direct stenting strategy including provisional predilatation is associated with long-term results as favorable as those associated with a systematic strategy of stenting after balloon predilatation. The 6-month MACCE and binary angiographic restenosis rates were comparable to those reported in recently published stent trials. [15] Long-term clinical outcomes cannot be compared with studies without protocol-mandated follow-up angiography, since the latter is highly sensitive in detecting restenotic lesions, leading to the performance of repeat PCIs in a higher percentage of patients.
On multivariate analysis a baseline serum CRP concentration >10 mg/L, expressed as a binary variable, was an independent predictor of angiographic restenosis and MACCE, suggesting that a detectable inflammatory activity is associated with tissue proliferative responses within successfully implanted stents. [22] As has been reported by others, post-procedural MLD, diabetes mellitus and triple vessel disease were independent predictors of restenosis and MACCE at six months. [23]
The clinical outcomes were similar in both treatment groups. However, from an economic point of view, there was a short-term advantage of direct stenting, due to a modest, though statistically significant reduction in procedural costs. At six month, a small cost advantage persisted in favor of direct stenting, although it was no longer

statistically significant as a result of the hugh variability in follow-up costs. This modestly lower cost associated with direct stenting has been reported by others. [1,3,6,9,11,12]

Limitations of the study

Angiographic follow-up was not complete since several patients refused to undergo the protocol-mandated catheterization procedure, although all patients underwent clinical follow-up examinations. In addition, these results reflect the performance of a single institution. However, this results in more uniformity to the study.

In conclusion, in this relatively unselected patient population, direct coronary stenting and stent implantation preceded by balloon dilatation were associated with equally high overall procedural success rates. Likewise, the 6-month MACCE, binary angiographic restenosis and target lesion revascularization rates were not different between the two treatment intentions, and similar to those reported in recently published stent trials. There was a short-term benefit conferred by direct stenting, attributable to a modest reduction in procedural costs. An elevated baseline CRP level was a predictor of adverse outcome after coronary stent implantation, suggesting that an enhanced inflammatory activity is associated with an intimal tissue proliferative response within successfully implanted stents.

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# Safety and efficacy of direct coronary stenting with a new balloon-expandable stent mounted on a rapid exchange delivery system, compared with stenting preceded by balloon dilatation
## The VELVET trial

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## Abstract

Aims of the study This study examined the 6-month angiographic results of direct coronary stenting, and compared the 9-month safety, efficacy and cost of this strategy versus stenting after balloon predilatation.

Patient populations, methods and results In phase I of VELVET, 122 patients (mean age=62.3±10.1 years, 77% men, 11% diabetics) with angina pectoris or myocardial ischemia due to a single de novo coronary stenosis of 51-95% underwent direct stenting. The endpoints of phase I included angiographic findings and rates of major adverse cardiac events up to 6 months of follow up. In phase II, 401 patients (mean age=61.3±10.8 years, 79% men, 16% diabetics) with angina pectoris or documented myocardial ischemia due to single or multiple, de novo or restenotic, coronary lesions were randomized between direct stenting and stenting after predilatation. The immediate angiographic results, and clinical outcomes and costs associated with the two treatment strategies up to 9 months of follow up were compared. In phase I the mean diameter stenosis immediately before and after the procedure, and at 6 months was 61.7±9.4%, 13.5±6.3%, and 33.6±16.2%, respectively. The 6-month binary restenosis rate was 11%. The overall rate of major adverse cardiac events, including 2 non cardiac deaths, was 9.8%. In phase II, the success rates of the intended delivery strategies were 87.9% and 97.9% for direct stenting and predilatation, respectively (P< 0.001), while the procedural success rates were similar (93.9 % vs. 96.5%). Over a mean follow up of 9 months, major adverse cardiac event (MACE) rates were 15.0% and 12.9% in patients randomized to direct stenting and predilatation, respectively (ns). Analyses of the costs incurred up to 9 months in each treatment group revealed a mean saving of Euros 362/patient in favor of the direct stenting strategy (ns).

Conclusions Compared with a strategy of stenting preceded by balloon dilatation, direct stenting was associated with an equivalent procedural success rate, equivalent clinical results up to 9 months of follow up, and a reduction in procedural and in-hospital costs (P<0.0001 and P<0.001, respectively), that was no longer significant after 9 months.

## Introduction

Considerable advances in coronary stent designs and delivery systems have prompted a growing number of interventional cardiologists to attempt the implantation of stents without prior balloon dilatation of the coronary lesion.[1-11] Besides its likelihood of being cost- and time-saving, this strategy offers the hypothetical advantages of causing less injury and less endothelial denudation by immediate scaffolding of the vessel wall, thereby facilitating reendothelialization. On the other hand, the direct and forceful implantation of the stent through the stenosis may be considerably more traumatic than its insertion after balloon predilatation. The ultimate balance of these opposing effects of direct stenting can only be reliably addressed by properly designed clinical trials. In recent randomized studies in patients with or without acute myocardial infarction, direct coronary stenting, though sometimes limited by high lesion complexity, has generally been found to be safe and effective, and associated with the use of fewer devices during the procedure, and shorter duration of the procedures.[1,3,6,9,11-17] Few studies, however, have separately examined the short- and long-term angiographic, clinical and economic results of direct coronary stenting.

The first objective of this study was to compare the safety and efficacy of direct stenting versus the delivery of a new balloon-expandable stent mounted on a rapid exchange delivery system preceded by dilatation of native coronary artery lesions. The second objective was to compare the medical resource consumption and costs incurred with each treatment method.

## Methods

### Patient population

This multicenter trial enrolled 523 patients with atherosclerotic disease of native coronary arteries between April 2000 and December 2000. A list of participating investigators from 10 European countries and the number of patients enrolled at each medical center is presented in the Appendix. The study was conducted in 2 phases. Phase I was non randomized and included 122 patients with single, de novo coronary stenoses of 51 to 95%, ≤ 15 mm in length in vessels ≥ 3.0 to 4.0 mm in diameter, who underwent direct stenting with the Bx VELOCITY™ Balloon-Expandable Stent (Cordis Corp., Johnson & Johnson, Warren, NJ, USA). This 6-month registry was designed to familiarize the operators with the use of the stent and its delivery system. It also provided an opportunity to measure the 6-month performance of the Bx VELOCITY™ stent by quantitative coronary angiography. Its endpoints included 1) cumulative incidence of major adverse cardiac events cerebrovascular accidents, and symptomatic ischemia at the 1-month visit, and major adverse cardiac events up to 6 months after the index procedure, and 2) angiographic findings at the time of the procedure and after 6 months by quantitative coronary analysis. Major adverse cardiac events was defined as

death from all causes, myocardial infarction, coronary artery bypass grafting, and further percutaneous target lesion interventions. In phase 2, 401 patients were randomized between direct stenting and stenting preceded by dilatation of single or multiple 51 to 95% de novo or restenotic lesion(s) ≤ 30 mm in length and 2.25 to 4.0 mm in diameter, which could be covered by 1 or 2 stents; these patients were followed clinically for 9 months after the index procedure, without the confounding effect of protocol-mandated follow up angiography. Its endpoints included 1) incidence of major adverse cardiac events, cerebrovascular accidents, and symptomatic ischemia at the 1-month visit, and major adverse cardiac events, including target vessel (instead of target lesion) revascularization at 9 months after the index procedure, 2) angiographic findings, at the time of the procedure, and 3) medical costs and cost-effectiveness up to 9 months after the index procedure. Delivery strategy success was defined as the successful implantation of the study stent, using the assigned treatment strategy, and achievement of <30% diameter stenosis by quantitative coronary analysis. Procedural success was defined as successful implantation of the study stent, achievement of <30% diameter stenosis by quantitative coronary analysis, and freedom from in-hospital major adverse cardiac events.

This study was approved by the Ethical Review Committees of all participating medical centers, and written informed consent was obtained from all patients. In both phases of the study, eligible patients were between the ages of 18 and 85 years of age and had stable angina or Braunwald Class B and C, I-II-III unstable angina,[18] or otherwise documented myocardial ischemia. Residual enzyme elevation from myocardial infarction within 72 h, intervention on other lesions within the preceding 30 days, unstable angina Braunwald Class A, I-II-III, a left ventricular ejection fraction ≤ 30%, serum creatinine > 3/0 mg/dL, chronic warfarin anticoagulation, and allergies to aspirin, clopidrogel, ticlopidine, or heparin, were clinical exclusion criteria in both phases. Procedural or angiographic exclusion criteria included unprotected left main coronary disease with ≥ 50% stenosis, pretreatment with a device other than an angioplasty balloon, stenting in saphenous vein grafts, in-stent restenosis, thrombi causing ≥ 50% stenosis within target lesion, TIMI grade 0 flow, a target lesion located at a bifurcation and requiring side branch stenting, > 50% stenosis proximal or distal to the target lesion treated during the same procedure, and the presence of a pre-existent stent within 5 mm of the target lesion.

### Randomization procedure

Following catheterization and identification of an eligible target lesion, patients were randomized by the data coordinating center, after obtaining informed consent and verification of all eligibility criteria by the investigator.

### Stents and delivery system, and procedural characteristics

In phase I, only 18 mm stents were available with diameters ranging from 2.5 to 4.0 mm, in increments of 0.25 mm. In phase II, investigators had a choice of stents that were 8 to 33 mm in length, in increments of 5 mm, with diameters ranging from 2.5

to 4.0 mm, in increments of 0.25 mm. The stents were mounted and crimped on the Raptor™ Rapid Exchange Delivery System (Cordis Corp.). Guiding catheters with an inner lumen diameter ≥ 0.064" were recommended for all procedures.
Percutaneous introduction of the guiding catheters and revascularizing devices, and predilatation procedures were performed according to standard procedures for each participating center, and remained unchanged throughout the study.

Peri- and postprocedural long-term drug therapy
Aspirin, 325 mg daily was administered at least once before the index procedure, and continued indefinitely thereafter. Heparin was administered during the procedure to maintain an activated clotting time > 250 sec, and discontinued within 12 h after the procedure. The use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. Clopidogrel in a loading dose of 300 mg followed by 75 mg daily, or ticlopidine, 250 mg twice daily, were begun before the procedure. Clopidogrel was continued in doses of 75 mg once daily, and ticlopidine in doses of 250 mg twice daily, each for 4 weeks.

Patient follow up
At 30 days and 6 months, patients enrolled in phases I and II, and at 9 months patients enrolled in phase II, returned for a physical examination, assessment of anginal status according to the Canadian Cardiovascular Society classification,[19] and recording of interim major adverse cardiac clinical events or coronary interventions. A 12-lead electrocardiogram was recorded at these visits, as well as other non-invasive tests, if clinically indicated. Patients enrolled in phase I also underwent 6-month follow up angiography for quantitative coronary analysis. The 6-month angiograms were waived in patients who had undergone an earlier unscheduled angiographic examination for clinical reasons.

Quantitative coronary angiography
All angiograms obtained during the index procedure in both patient groups, and at 6 months in patients enrolled in phase I, were analyzed by an independent core laboratory (Cardialysis, Rotterdam, The Netherlands). The measurements included assessment of TIMI flow grade, presence of thrombus, lesion length, eccentricity, and calcification, American Heart Association/American College of Cardiology class, and dissection grade. Restenosis was defined as a luminal narrowing ≥ 50 % at 6 months in phase I patients. Minimum luminal diameter and %DS were measured both "in-stent", i.e. within the stent borders, and "in-segment", i.e. within the vessel segment defined by side branches bounding the stented segment. All unscheduled angiograms prompted by return of symptoms, abnormal stress testing, or other untoward coronary events, were also submitted to Cardialysis for quantitative coronary analysis.

Cost analysis
Collection of costs and cost effectiveness data was limited to direct medical costs. Comparisons of resource utilization between the 2 treatment strategies included costs

of the initial procedure, and resources used until discharge from the hospital and up to 9 months of follow up in phase II. The primary goal of the economic evaluation was to assess the probability that direct stenting combines added effectiveness with cost savings compared to stenting with predilatation. Additional assessments included the probability that direct stenting is less effective though less costly, more effective and more costly, or less effective and more costly than stenting and predilatation.

### Safety, events and data monitoring

A Data and Safety Monitoring Board reviewed the data to identify any potential safety issues. Members of this Board were not affiliated with the study sponsor. An Endpoint Review Committee comprising two independent physicians and one VELVET investigator adjudicated and confirmed the classification of major adverse cardiac events and cerebrovascular events.

### Statistical analyses

An enrolment of 520 patients was planned for this study. Ultimately, 122 patients were included in phase I, and 401 were randomized in phase II. This latter sample size was expected to detect a minimum treatment difference of 9% in the primary endpoint with an 80% power, including a 10% loss to follow-up, and a two-sided significance level set at 0.05. All efficacy and safety analyses were performed on an intention-to-treat basis.
Efficacy analysis in phase II The proportion of patients who reached a 30-day primary endpoint was calculated in each treatment group and tested for equivalence by the Farrington-Manning method.[20] Quantitative angiographic results from the core laboratory were summarized for each treatment group and time point. Between-groups comparisons were performed by one-way analysis of variance.
Safety analysis in phase II All major adverse cardiac events occurring in each treatment group before hospital discharge, and at 30 days and 9 months after the index procedure were counted, and presented in a hierarchical order. The Kaplan-Meier life-table method was used to analyze time to clinical events. Comparisons of the event-free survival curves in the two phase II treatment groups were made using the Wilcoxon and log-rank tests at 9 months of follow up.
Costs in each treatment group were calculated by multiplying resource utilization with unit costs from the Netherlands. Differences in costs were compared by Student's t-test and Wilcoxon rank order statistic. The probability of both difference in costs and difference in effects being in the 4 quadrants of the cost-effectiveness plane was assessed by calculating (by a Gaussian method) the appropriate densities, using the bivariate normal distribution of both average costs and average effects.
All computations were performed with the SAS® (SAS Institute) and EquivTest (Statistical Solutions) software packages. Values are presented as mean ± standard deviation (SD). A two-sided P value $< 0.05$ was considered statistically significant.

## Results

Table 1. Baseline characteristics of 122 patients enrolled in phase I of VELVET

| | |
|---|---|
| Age, y (mean±SD) | 62.3±10.1 |
| Men/Women | 77/23 |
| Diabetics | 11 |
| Previous/current smoking history | 42/25 |
| Treated hypercholesterolemia | 49 |
| Treated hypertension | 53 |
| Previous myocardial infarction/coronary surgery/angioplasty | 34/2/17 |
| Braunwald classes I/II/III unstable angina pectoris | 16/21/12 |
| Canadian Cardiovascular Society classes I/II/III/IV stable angina pectoris | 4/21/10/1 |
| Silent ischemia | 12 |
| Number of diseased coronary arteries | |
| 1 | 68 |
| 2 | 21 |
| 3 | 11 |
| Reference vessel diameter, mm (mean±SD, range) | 2.80±0.56, 1.85-4.45 |
| Lesion length, mm (mean±SD, range) | 10.25±3.64, 3.40-24.17 |
| Lesion location | |
| Right coronary artery | 31 |
| Left anterior descending artery | 50 |
| Left circumflex artery | 19 |

Unless otherwise indicated, values are percentages of 122 patients

## Phase I

The baseline characteristics of the 122 patients enrolled in phase I of VELVET are presented in table 1. The overall success of the intended treatment strategy was 91.8%, and the ultimate procedural success rate was 95.1%. The main cause of delivery strategy failure was the need for predilatation in 8.2% of patients, because of failure of the stent device to cross the lesion in 7.4% of cases. The mean duration of hospitalization for the index procedure was 2.5±1.2 days. The angiographic follow up at 6 months included 99 of the 122 patients (81%). Causes for missing follow up angiograms included death (n=2), and patient refusal (n=21). Table 2 presents the angiographic measurements performed immediately before and after the index procedure, and at 6 months. The restenosis rate among 99 patients who underwent follow up angiography at 6 months was 11%.

Table 2. Results of quantitative coronary analysis and major adverse events at 1 month and 6 months in 122 phase I patients

| Measurement (n = number of observations available for analysis) | | P |
|---|---|---|
| Reference vessel diameter, mm (n) | | |
| Before procedure | 2.80±0.56 (122) | - |
| After procedure | 2.95± 0.46 (121) | 0.0001 |
| 6 months | 2.79± 0.62 (97) | 0.672 |
| MLD, mm (n) | | |
| Before procedure | 1.06±0.34 (122) | - |
| After procedure | 2.55±0.41 (121) | 0.0001 |
| 6 months | 1.85±0.60 (99) | 0.0001 |
| Percent diameter stenosis (n) | | |
| Before procedure | 61.7±9.4 (122) | - |
| After procedure | 13.5±6.3 (121) | 0.0001 |
| 6 months | 33.6±16.2 (99) | 0.0001 |
| Immediate gain, mm (n) | 1.48±0.40 (121) | - |
| Late loss, mm (n) | 0.70±0.43 (99) | - |
| Total occlusion, % (n) | 2 (99) | - |
| Binary restenosis rate, % (n) | 11 (99) | - |
| Adverse events (hierarchical order) | N (% of patients) | |
| 0-30 DAYS CLINICAL EVENTS | | - |
| Death | 1 (0.8) | - |
| Cardiac | 0 | - |
| Non cardiac | 1 (0.8) | - |
| Cerebrovascular Accident | 0 (0) | - |
| Myocardial infarction | 3 (2.5) | - |
| Q-wave | 1 (0.8) | - |
| non Q-wave | 2 (1.6) | - |
| Coronary bypass surgery | 0 | - |
| Percutaneous target lesion revascularization | 1 (0.8) | - |
| Symptomatic ischemia | 6 (5.0) | - |
| Major adverse cardiac and cerebrovascular events | 5 (4.1) | - |
| OVERALL PRIMARY ENDPOINT* | 11 (9.1) | - |
| 0 -180 DAYS MAJOR ADVERSE CARDIAC EVENTS | | |
| Death | 2 (1.6) | - |
| Cardiac | 0 | - |
| Non cardiac | 2 (1.6) | - |
| Myocardial infarction | 4 (3.3) | - |
| Q-wave | 1 (0.8) | - |
| non Q-wave | 3 (2.5) | - |
| Coronary bypass surgery | 3 (2.5) | - |
| Percutaneous target lesion revascularization | 3 (2.5) | - |
| OVERALL MAJOR ADVERSE CARDIAC EVENTS | 12 (9.8) | - |

*Primary endpoint phase 1 = symptomatic ischemia at the 1-month visit or major adverse cardiac events and cerebrovascular accidents at 30 days.
MLD = mean minimal luminal diameter
P values refer to comparisons with measurements before procedure

Early and long-term clinical events

At a mean follow up of 37±17 days, stable (n=4) or unstable (n=2) angina had returned in 5% of 120 analyzable patients (table 2). Table 2 also lists the numbers of major adverse cardiac events, including 2 non cardiac deaths, recorded between the index procedure and 180 days. Two patients died, one of rapidly evolving lung carcinoma at 110 days, and the other of profound ticlopidine-induced thrombocytopenia at 23 days. The overall freedom from major adverse cardiac events and free from target lesion revascularization at 6 months in phase I patients was 90.2% and 93.4%, respectively. By multivariate analysis, among 34 demographic, clinical and angiographic variables tested, type IIb eccentricity of the lesion (odds ratio: 8.05, P=0.055) and minimum luminal diameter after stent implantation (odds ratio: 0.131, P=0.053) were independent predictors of major adverse cardiac events, and > 1 stent implanted (odds ratio: 85.97, P=0.006), hypercholesterolemia (odds ratio: 16.96, P=0.005), and minimum luminal diameter after stent implantation (odds ratio: 0.007, P=0.01) were independent predictors of restenosis.

## Phase II

The baseline characteristics of the 401 patients enrolled in phase II of VELVET, and of each treatment group separately, are presented in table 3. There was no difference between the 2 treatment groups. The mean duration of hospitalization for the index procedure was 2.6±1.8 days (range 2-24) in the predilated group versus 2.7±2.5 days (range 1-33) in the directly stented group. The success of the intended delivery strategy per lesion treated was 97.9% for predilatation versus 87.9% for direct stenting (P <0.001), while the procedural success rates per patient treated were similar (96.5% vs. 93.9%). The main reason for the significant difference in the success rates of the intended strategy between the 2 groups was due to the need to predilate 22 of 240 (9.2%) treated lesions in the direct stenting group. The results of quantitative coronary analysis after the index procedure in the 2 randomized groups are shown in table 4. Except for a slightly greater in-stent %DS in the direct stenting group (P <0.02), no significant difference was observed between the 2 groups in the immediate angiographic outcomes. The cumulative distribution of postprocedural in-stent %DS in each treatment group is shown in figure 1. Coronary artery dissections occurred in 8.7% of direct stenting procedures, versus 25.8% of procedures preceded by balloon dilatation (P<0.01).

By multivariate analysis of the results in the direct stenting group, dissection at the treated site during attempted direct stenting (odds ratio: 0.182, P=0.026), younger age (odds ratio: 0.945, P=0.012), and a history of previous coronary artery bypass graft (odds ratio: 0.206, P =0.016) were independent negative predictors of direct stenting strategy success.

Table 3. Baseline characteristics of patients randomized in phase II of VELVET

| Characteristic | Direct stenting (n=200) 243 lesions | Predilated (n=201) 240 lesions | All patients (n=401) 483 lesions |
|---|---|---|---|
| Age, y (mean±SD) | 61.4±11.1 | 61.1±10.5 | 61.3±10.8 |
| Men/Women | 82/18 | 77/23 | 79/21 |
| Diabetics | 17 | 15 | 16 |
| Previous/current smoking history | 37/34 | 35/29 | 36/31 |
| Treated hypercholesterolemia | 48 | 45 | 46 |
| Treated hypertension | 54 | 57 | 56 |
| Previous MI/CABG/angioplasty | 46/6/21 | 36/3/12 | 41/4/17 |
| Braunwald classes I/II/III unstable AP | 10/24/14 | 9/22/15 | 10/23/15 |
| CCS classes I/II/III/IV stable AP | 4/22/11/1 | 5/27/9/0 | 4/24/10/1 |
| Silent ischemia | 10 | 10 | 10 |
| Number of diseased coronary arteries | | | |
| 1 | 58 | 57 | 58 |
| 2 | 28 | 29 | 29 |
| 3 | 14 | 14 | 14 |
| # of lesions/patient (mean±SD) | 1.2±0.5 | 1.2±0.5 | 1.2±0.5 |
| Lesion location | | | |
| Right coronary artery | 28 | 30 | 29 |
| Left anterior descending artery | 42 | 46 | 44 |
| Left circumflex artery | 29 | 24 | 27 |
| Preprocedural TIMI grade | | | |
| 0 | 0 | 0 | 0 |
| I | 1 | 2 | 2 |
| II | 18 | 11 | 14 |
| III | 81 | 87 | 84 |
| ACC/AHA lesion classification | | | |
| Type A | 5 | 5 | 5 |
| Type B1 | 36 | 31 | 34 |
| Type B2 | 55 | 62 | 59 |
| Type C | 3 | 2 | 2 |

MI = myocardial infarction; CABG = coronary artery bypass graft; AP = angina pectoris; CCS = Canadian Cardiovascular Society; ACC/AHA = American College of Cardiology/American Heart Association
Unless otherwise indicated, values are percentages of patients

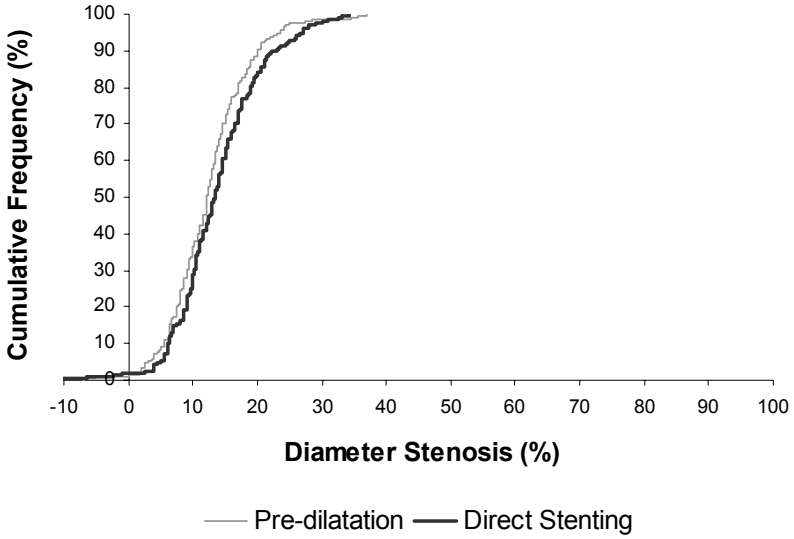



Figure 1. Cumulative distribution of postprocedural %DS in both treatment groups of phase II.

One-month clinical results

At a mean of 38±25 days after the index procedure, stable and unstable angina had returned in 6.1% and 1.5%, respectively, of 196 patients randomized to predilation, versus 5.7% and 2.1%, respectively, of 192 patients randomized to direct stenting (ns). Likewise, no difference was found between the 2 groups at 1 month in overall rates of major adverse cardiac events (3.0% in both groups, table 4). Two patients randomized to predilatation died out of the hospital due to presumed stent thrombosis and of cerebrovascular accident 3 days and 25 days after the index procedure, respectively. One patient randomized to direct stenting died of presumed stent thrombosis 28 days after the index procedure, respectively.

By multivariate analysis of the results in the overall population, male gender (odds ratio: 0.323, P <0.001), unstable angina (odds ratio: 2.526, P=0.005), history of coronary artery bypass graft (odds ratio: 4.154, P=0.015 and > 1 implanted stent (odds ratio: 3.442, P=0.01), were independent predictors of recurrent ischemic events at the 1-month visit, and/or major adverse cardiac events and cerebrovascular accident at 30 days.

Table 4. Results of postprocedural quantitative coronary angiographic analysis, and cumulative major adverse cardiac events up to 1 month and 9 months in 200 patients randomized to direct stenting and 201 patients randomized to stenting preceded by balloon angioplasty

| QUANTITATIVE CORONARY ANGIOGRAPHIC ANALYSIS MEASUREMENT | Direct stenting (n=200) 243 lesions | Predilated (n=201) 240 lesion |
|---|---|---|
| Reference vessel diameter, mm (mean±SD) | 2.83±0.47 | 2.86±0.49 |
| In-stent % diameter stenosis* | 13.9±6.8 | 12.5±6.3 |
| In-segment % diameter stenosis | 25.1±10.1 | 24.4±10.2 |
| In-stent MLD, mm (mean±SD) | 2.43±0.43 | 2.49±0.43 |
| In-segment MLD (mean±SD) | 2.05±0.48 | 2.06±0.49 |
| Adverse events (hierarchical order) | Direct stenting | Predilated |
| 0 – 30 DAYS | | |
| Death | 1 (0.5) | 2 (1.0) |
| Cardiac | 1 (0.5) | 1 (0.5) |
| Non cardiac | 0 | 1 (0.5) |
| Cerebrovascular accident | 0 | 0 |
| Myocardial infarction | 4 (2.0) | 4 (2.0) |
| Q-wave | 1 (0.5) | 1 (0.5) |
| non Q-wave | 3 (1.5) | 3 (1.5) |
| Coronary bypass surgery | 0 | 0 |
| Percutaneous target vessel revascularization | 1 (0.5) | 0 |
| Symptomatic ischemia | 12 (6.3) | 14 (7.1) |
| Major adverse cardiac and cerebrovascular events | 6 (3.0) | 6 (3.0) |
| OVERALL PRIMARY ENDPOINT** | 18 (9.3) | 20 (10.1) |
| 0 - 270 DAYS | | |
| Death | 2 (1.0) | 2 (1.0) |
| Cardiac | 2 (1.0) | 1 (0.5) |
| Non cardiac | 0 | 1 (0.5) |
| Myocardial infarction | 8 (4.0) | 7 (3.5) |
| Q-wave | 2 (1.0) | 3 (1.5) |
| non Q-wave | 6 (3.0) | 4 (2.0) |
| Coronary artery bypass graft surgery | 3 (1.5) | 1 (0.5) |
| Percutaneous target vessel revascularization | 11 (5.5) | 12 (6.0) |
| OVERALL MACE | 24 (12.0) | 22 (10.9) |

Unless indicated otherwise, values represent numbers (%) of patients

* $P < 0.02$

** Primary endpoint phase 2 = symptomatic ischemia at the 1-month visit or major adverse cardiac events and cerebrovascular accidents at 30 days.

MLD = minimalum luminal diameter; MACE = major adverse cardiac events

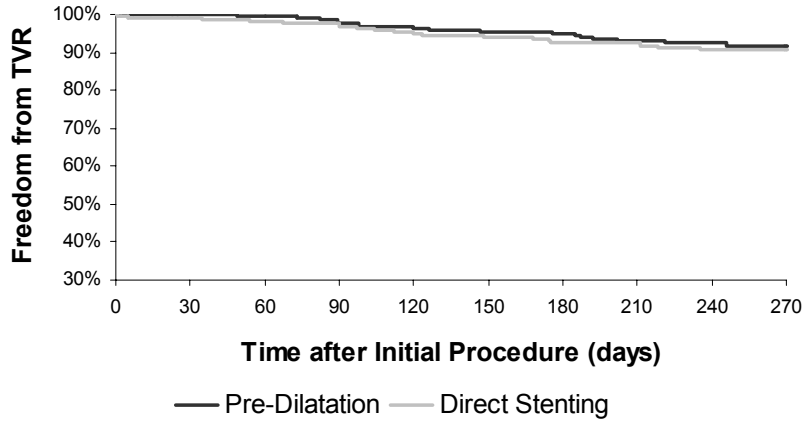
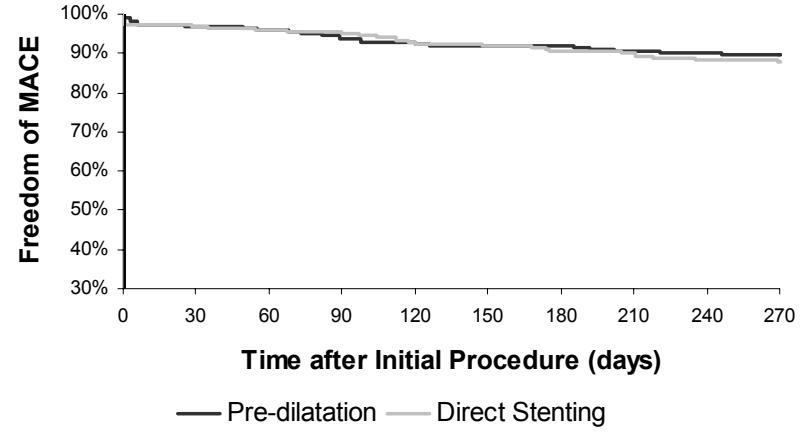



Figure 2.
A. Kaplan-Meier survival free from target vessel revascularization in Phase II of VELVET




B. Kaplan-Meier survival free from major adverse cardiac events in Phase II of VELVET

Long-term adverse clinical events

At 270 days after the index procedure, major adverse cardiac events had occurred between 30 days and the end of follow up in 30 of 200 (15.0%) patients randomized to direct stenting, versus 26 of 201 (12.9%) patients randomized to predilatation (ns, table 4). One patient randomized to direct stenting died of acute thrombotic occlusion in a non-target vessel after an intracoronary ultrasound examination, 269 after the index procedure. The cumulative survival free from target vessel revascularization in each patient group is presented in figure 2A, and the major adverse cardiac events-free survival is shown in figure 2B. Neither analysis showed a difference between the 2 groups.

Table 5. Comparisons of procedural, hospitalization, and follow up costs in phase II of VELVET

| Cost item | Direct Stenting | Predilatation |
|---|---|---|
| Procedure time (minutes) | 1079 | 1159 |
| Balloon catheter | 133 | 596 |
| Bx-Velocity™ stent | 870 | 892 |
| Guiding catheter | 115 | 123 |
| Guide wire | 129 | 135 |
| Contrast material | 102 | 108 |
| Non study stent | 7 | 7 |
| Miscellaneous | 86 | 80 |
| PROCEDURAL COSTS | 2521 | *3100 |
| Hospital costs | 1336 | 1301 |
| TOTAL IN-HOSPITAL COSTS | 3857 | **4401 |
| Follow up costs | 2841 | 2659 |
| OVERALL 9-MONTH COSTS | 6698 | ***7060 |

Values represent mean cost per patient (± SD) in Euros
Mean procedure times in min were 59.3 in the direct stenting group, versus 63.8 in the predilated group.
*P<0.0001; **P<0.001; ***NS

Cost analysis

The mean procedural, hospitalization and long-term costs calculated per patient in each treatment group are listed in table 5. The mean overall procedural cost per patient was Euros 579 lower in the direct stenting than in the predilatation group (P=0.0001 Wilcoxon; P<0.0001 t-test) (figure 3A). Most of the cost-saving calculated in the direct stenting group was attributable to the lower use of angioplasty balloons (Euros 463). At the time of discharge from the hospital, the average cost per patient was Euros 3857 in the direct stenting group, versus Euros 4401 in the predilated group. (P=0.0001 Wilcoxon; P<0.001 t-test). Between discharge of the patients from the hospital and the end of follow up, mean costs per patient were Euros 182 higher in patients randomized to direct stenting than to predilatation. The higher costs in the direct stenting group during follow up were mostly attributable to the surgical and hospitalization costs incurred by 4 patients undergoing coronary artery bypass graft surgery, in contrast to a single patient in the predilated group. At 9 months, overall costs per patient were Euros 6698 in patients randomized to direct stenting versus Euros 7060 in patients randomized to predilatation (Wilcoxon p = 0.0171; t-test p=0.5149). The absence of a significant difference by t-test was due to the wide dispersion in costs incurred in both groups during long-term follow up. The probability of direct stenting being more effective and less costly was 31.5% while the probability of stenting after predilatation being more effective and less costly was 21.7% (figure 3B).

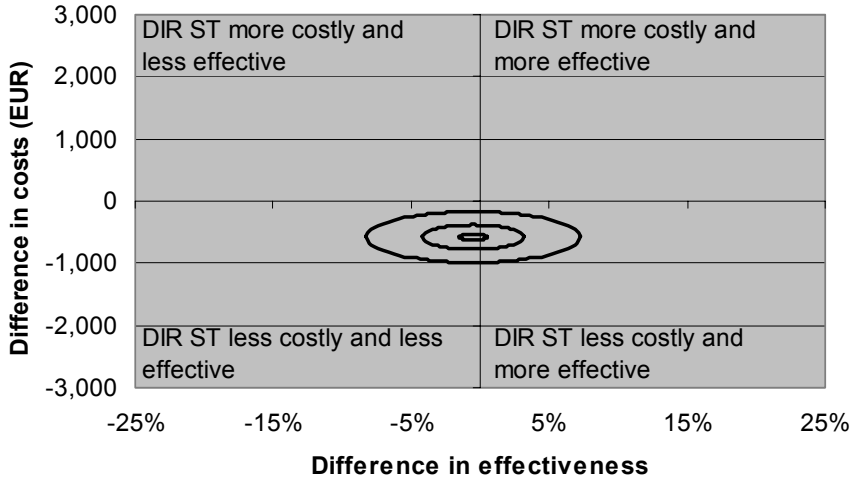
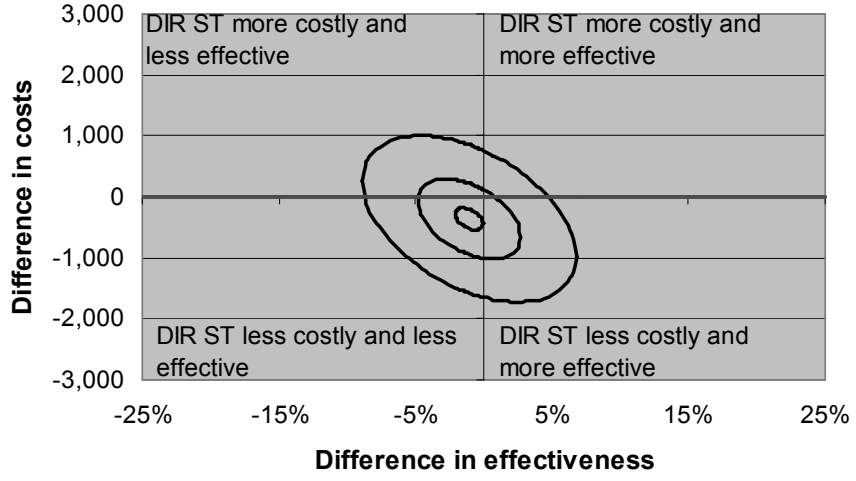



Figure 3.
A. Procedure-related cost-effectiveness analysis of direct stenting (DIR ST) versus predilatation. Inner ellipse = 5% probability; middle ellipse = 50% probability; outer ellipse = 90% probability. EFF = effective.




B. Cost-effectiveness analysis of direct stenting (DIR ST) versus predilatation up to 270 days. Abbreviations as in figure 3A.

## Discussion

The sequential design of this study, which included a non randomized followed by a randomized phase, allowed us to separately 1) examine the 6-month angiographic outcomes of the direct stenting strategy, and 2) compare its effects on clinical events and medical costs up to 9 months with a standard approach of stenting preceded by predilatation, without the confounding influence of protocol-mandated follow up angiography.

### Safety and efficacy in phase I

The non randomized phase of VELVET confirmed that, in properly selected patients, a primary delivery strategy success rate in excess of 90% can be achieved with direct stenting. The final procedural success rate, including the few patients in whom balloon predilatation was needed, was equivalent to that typically observed with standard methods in this type of patient population. More importantly, there seemed to be no negative effect of direct stenting on the long-term angiographic or clinical results in this group of patients. The low 6-month restenosis (11%) and target lesion or vessel revascularization (6.6%) rates are particularly noteworthy, and considerably below what was predicted by multivariate analysis based on models derived from comparable populations. In the absence of a clear explanation for this unexpected result we can only hypothesize that a somewhat skewed data distribution of the %DS at follow up in a relatively small sample size, with seven out of 99 patients having a %DS between 45% and 49%, may have yielded a lower than predicted 6-month restenosis rate. Had these patients been counted as cases of restenosis, the rate would have been 17%.

As typically seen in this type of analysis, postprocedural minimum luminal diameter and multiple stents were predictors of restenosis. Lesion eccentricity (type IIb of the Ambrose classification),[21] an angiographic marker of higher instability, importantly emerged as an independent risk factor for major adverse cardiac events associated with direct stenting. In contrast, unstable angina, was associated with a higher success rate of direct stenting, possibly due to a lower resistance to passage of the catheter offered by unstable lesions.

### Safety and efficacy in phase II

The primary success rate of the intended implantation method was significantly higher in patients randomized to predilatation than to direct stenting. However, the procedural success rates of the 2 methods were similar, and equivalent to the final success rate measured in phase I. From the results of phases I and II, the incremental success rate conferred by balloon predilatation is approximately 5%. As in phase I, rates of long-term major adverse cardiac events were comparably low in both treatment groups in phase II, confirming that a systematic direct stenting with provisional predilatation strategy is associated with long-term results as favorable as those associated with a systematic strategy of balloon predilatation.

The entry criteria for this study, which was designed to evaluate the application of direct coronary stenting in a wide spectrum of lesions, were intentionally non restrictive. No preprocedural angiographic characteristic was retained as an independent predictor of success of delivery strategy in the multivariate analysis, although moderate-to-heavy calcification was a negative predictor in the univariate analysis.

Cost analysis

An expected advantage of direct coronary stenting, as opposed to stenting after predilatation, is the use of fewer balloon catheters and related devices, of smaller quantities of contrast material, and a shorter stay in the catheterization laboratory.[22] This expectation has generally been confirmed in previous studies.[1,3,6,9,11-17] However, the results of formal cost analyses have been mixed. Except in one study,[16] procedural costs were only modestly reduced, as was observed in this study.[12,15,] Furthermore, this study, uniquely designed to compare costs in a population whose long-term management is similar to standard clinical practice, is the first to report results beyond the in-hospital phase of the treatment. While a small advantage persisted in favor of direct stenting at 9 months, the difference was no longer significant due to the considerable costs resulting from additional hospitalizations and procedures during long-term follow up, and increase in the variability of costs among patients of both groups.

In conclusion, in this selected patient population, stent delivery preceded by balloon dilatation and direct coronary stenting yielded similar overall procedural success rates. When direct stenting failed, the intervention typically proceeded uneventfully with standard techniques, including predilatation. The 1-month rate of the composite endpoint of ischemic symptoms and/or major adverse cardiac events and cerebrovascular accidents, and the 9-month major adverse cardiac event rates were similar in both treatment groups. The procedural success and major adverse cardiac events rates observed in the non randomized phase of the study were similar to those measured in phase II. Finally, the significant cost saving attributable to the direct stenting strategy that was evident post procedure and after 30 days, was no longer significant after 9 months.

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# Appendix

The following Investigators and Institutions participated in phases I and/or II of VELVET. The total number of patients enrolled at each center is also indicated in parenthesis
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# Impact of operator volume on overall major adverse cardiac events following direct coronary stent implantation versus stenting after predilatation

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## Abstract

Objectives: To determine the impact of operator experience on procedural, clinical and angiographic outcome after (direct) coronary stent implantation.
Background: Although for other forms of percutaneous coronary interventions an inverse relationship between operator volume and patient outcomes has been shown, the impact of operator volume on outcome after direct stenting has never been investigated.
Methods: We performed an analysis on data from a prospective randomized trial comparing direct stenting with that after predilatation. The trial consisted of 400 patients with stable and unstable angina pectoris and/or myocardial ischemia due to a coronary stenosis of a single native vessel eligible in 1999-2001 for direct stenting. For a single center high volume clinic (>1500 cases/yr.), we compared the most experienced operators (caseload: > 4000) with well-trained fellows (caseload: >75). We identified 115 patients who were treated by high-volume and 180 patients treated by lower-volume operators.
Results: Baseline patient characteristics were evenly distributed among groups. High-volume compared to lower-volume operators, were faster (30.8 vs. 42.2 min, $p<0.001$), needed less frequent postdilatation (15 vs. 24%, $p=0.06$) and had lower fluoroscopy times (7.5 vs. 11.2 min, $p<0.001$), lower contrast usage (180 vs. 228 ml, $p<0.001$), lower procedural costs (Euros 1982 vs. 2164, $p=0.05$) and reduced rates of major adverse cardiac and cerebral event (MACCE) at six month (12.2 vs. 21.1%, $p=0.03$). The lower-volume operator group experienced higher angiographic binary restenosis rates after direct stenting compared to stenting after predilatation (31.5 vs. 14.9%, $p=0.005$).
Conclusions: Stenting performed by high-volume operators resulted in a 50% reduction in MACCE as compared to lower-volume physicians, which also had twice as much restenosis when using direct stenting. Hence, the more demanding technique of direct stenting should be reserved for high-volume operators. Furthermore, prolonged training periods and even more intensive supervision by experienced operators seems mandatory.

## Introduction

It is well known that surgical procedures performed by inexperienced operators are associated with an increased patient morbidity and mortality rate [1-5]. Recently it has also been established that there is an inverse relationship between the annual volume of percutaneous coronary interventions (PCI) and the incidence of procedural complications at the operator level [6-13]. The strongest relationship in this respect exists for the incidence of emergency coronary artery bypass surgery (CABG). In general, at both institutional and operator level, higher PCI volumes have been associated with significant reductions in the need for postprocedure CABG [14-18].

However, controversy exists in the field of cardiology regarding the importance of experience for PCI with coronary stent procedures. The impact of operator performance on long-term outcome after coronary stent implantation has never been investigated. Furthermore, the relationship between operator volume and clinical outcome after application of the more demanding but increasingly applied technique of direct stenting, i.e. stenting without predilatation, is not clear. Recent studies of direct stenting have confirmed its feasibility and safety in selected patients, but randomized controlled trials failed to prove large significant differences in procedural times, fluoroscopy times, material costs or long-term major adverse cardiac and cerebral events (MACCE) and angiographic restenosis rates [19-29].

We therefore compared the impact of high-volume with lower-volume operators, on the angiographic and clinical outcome following direct coronary stent implantation or stenting after predilatation, in patients with single vessel PCI.

## Methods

### Patient population

We performed a prospective subgroup analysis using the INSTANT database, which consists of 400 eligible patients with stable or unstable angina pectoris and/or myocardial ischemia due to a non occlusive coronary stenosis of a single native vessel without a chronic total vessel occlusion, an ostial lesion, a lesion at a bifurcation, or a densely calcified lesion. The primary goal of the INSTANT trial was to compare the effect of direct stenting versus stenting after predilatation on clinical and angiographic outcome. All patients had been randomized 1:1 to either direct stenting or balloon predilatation by a computer-based randomization program.

Current ACC guidelines recommend that physicians perform at least 75 PCIs annually and a hospital volume of at least 400 procedures/ yr. to ensure good outcomes [30]. Our analyses included highly experienced operators on the one hand (minimum case load: 4000; 200-400 cases/yr.), and well trained fellows on the other (minimum case load: 75), all working in a tertiary interventional center with a hospital volume of more than 1500 procedures per year. The well-trained fellows could any moment ask for supervision of experienced interventional cardiologists.

Patients treated by operators who met the volume criteria mentioned above were selected for analysis. We identified 115 patients who were treated by high-volume operators and 180 patients treated by lower-volume physicians between January 1999 and June 2001.

Stent implantation procedure

All interventional cardiologists or fellows treating study patients adhered to the same study protocol. All patients received aspirin, 500 mg before, and clopidogrel, 300 mg, after the procedure to all patients. Heparin, 10.000 U, was given in an intravenous bolus at the beginning of the procedure, followed by additional hourly boluses of 5000 U. The use of glycoprotein IIb/IIIa receptor antagonists was left to the operators' discretion. The target lesion was accessed by standard techniques using the transradial, transfemoral, or transbrachial approach, and 6-F guiding catheters with appropriate curves were used. The target lesion was crossed with a 0.014-inch coronary guidewire. When performing pre- or postdilatation, balloons of the shortest possible length were chosen to minimize the extent of vessel wall injury.

An AVE S670 stent (Medtronic Inc. Minneapolis,U.S.A.) mounted on a rapid exchange delivery balloon was used in all procedures. Stents as short as possible were chosen to avoid unnecessary wall coverage, and sizes were selected to reach a 1.1 to 1.2 stent/artery ratio. The burst pressure rating of the delivery balloon is 16 atm. The balloon pressure for final stent expansion was ≥ 14 atm. The use of additional postdilatation balloons was left to the operator's discretion, though not encouraged, and the implantation of multiple stents was discouraged. Crossover from direct stenting to predilatation was permitted when the stent could not be advanced through the stenosis. In such cases, standard balloon predilatation was performed, followed by further attempts to cross the lesion with the stent.

Quantitative coronary angiography

At each procedure, pre- and post-stenting angiographic images were obtained in at least two reproducible orthogonal views, free of vessel overlapping and foreshortening, for computer-assisted QCA analysis. Intracoronary nitroglycerine, 100-300 μg, was injected before each cineangiographic recording, which were made before balloon dilatation, and/or immediately before and after stent implantation. During filming, the catheter tip had to be empty of contrast agent, the patient in mid inspiration, and the table immobile. All angiograms were stored in a computer database and analyzed off-line, using the CAAS '99 Camtronics (Philips Medical System, Eindhoven, the Netherlands), and analyzed by an independent observer, according to an established protocol (Cardialysis, Rotterdam, the Netherlands). Regions of interest were chosen in the target vessel, and measurements of reference vessel diameter, minimal luminal diameter (MLD) and percent diameter stenosis (%DS) were made on end-diastolic frames. Lesion types were graded according to the American College of Cardiology/American Heart Association lesion characteristics classification. Lesion length, in mm, was measured as the distance between proximal and distal shoulders of the lesion. Proximal tortuosity

was defined as the presence of 2 or more bends each> $45^0$, proximal to the lesion. Binary restenosis was defined as a luminal narrowing ≥ 50% at 6 months. MLD and %DS were measured within the stent's edges.

Endpoint definitions

The primary endpoint of this investigation was to compare upto six months the composite incidence of major adverse cardiac and cerebral events (MACCE) for high-volume and lower-volume operators. MACCE was defined as death from all causes, myocardial infarction (MI), repeat target- and non-target-vessel-related percutaneous coronary intervention (PCI), target lesion revascularization (TLR), coronary artery bypass grafting (CABG) and stroke. Revascularization of the target lesion was defined as PCI or CABG performed for restenosis of the target lesion in association with recurrent angina, objective evidence of myocardial ischemia or both. Diagnosis of MI was based on 1) prolonged typical chest pain associated with 2) either new pathological Q-waves >0.03 s in duration in the electrocardiogram, or 3) with a rise in troponine I, creatine kinase (CK) enzyme or its MB fraction above twice the upper limit of normal value (CK >200U/L; MB >20U/L). Two of the three clinical findings had to be present.

Additional endpoints were successful direct stenting, procedural success, occurrence of dissection, need for postdilatation, procedural time, fluoroscopy time, use of contrast agent, procedural costs and angiographic six-month binary in-stent restenosis. Successful direct stenting was defined as a successful procedure without the need for predilatation. Procedural success was defined as TIMI grade III flow [31], final residual in-stent %DS < 30%, and absence of MACCE during the index hospitalization. The angiographic endpoints were already defined above.

Patients follow-up

All patients had undergone clinical follow-up for recording of MACCE, coronary intervention, or clinical manifestations consistent with recurrent myocardial ischemia. Of analyzed patients 85% had also undergone follow up angiography for QCA at six months. Reason for absence of six month coronary angiogram were death or patient`s refusal.

Direct stenting versus predilatation

To investigate the impact of operator experience on the effect of direct stenting on clinical and angiographic outcome we also compared patients randomized to direct stenting with patients randomized to stenting after predilatation per operator group. Outcome parameters were procedural success, cumulative MACCE to six months and angiographic binary restenosis.

Statistical analysis

For comparison of continuous non-paired variables between the treatment groups, the unpaired two-tailed Student's t test was used or, in case of skewed data, the Mann-Whitney U-test. Comparison of categorical variables or composite clinical endpoints (any

MACCE) was performed using the Pearson Chi-square test. Continuous variables were expressed as mean±SD, and/or as percentages. Statistical tests were carried out with the SPSS 8.0 and 10.0 statistical software package (Chicago, IL).

## Results

Table I. Baseline characteristics of patients treated by high-volume operators compared to lower-volume operators.

| BASELINE CHARACTERISTICS | HIGH-VOLUME | LOW-VOLUME |
|---|---|---|
| Number of patients | 115 | 180 |
| Age, years (mean±SD) | 61±11 | 60±11 |
| Men/Women | 80/20 | 82/18 |
| Diabetics/smoking/hypertension/ hypercholesterolemia | 13/45/40/61 | 16/31/32/58 |
| Prior MI/PCI/CABG | 40/21/11 | 31/12/4 |
| Anginal CCS classes I/II/III/IV | 4/18/46/32 | 5/21/42/32 |
| Number of diseased coronary arteries (1/2/3) | 65/24/11 | 70/19/11 |
| Direct stenting/ predilatation technique | 50/50 | 49/51 |
| Number of treated lesions | 133 | 217 |
| Lesion location | | |
| Left Anterior Descending artery | 41 | 39 |
| Circumflex Artery | 24 | 27 |
| Right Coronary Artery | 35 | 34 |
| ACC/AHA lesion classification¶ type A/B1/B2/C | 27/37/21/15 | 20/45/27/8 |
| TIMI grade flow 0/I/II/III | 2/4/3/91 | 0/3/4/93 |
| Proximal tortuosity | 44 | 36 |
| Lesion calcification | 13 | 8 |
| Sidebranch involved | 37 | 31 |
| Lesion length, mm (mean±SD) | 9.8±4.7 | 8.8±3.7 |
| Reference diameter, mm (mean±SD) | 2.9±0.6 | 2.9±0.6 |
| Minimal lumen diameter, mm (mean±SD) | 1.0±0.37 | 1.0±0.31 |
| Stenosis, % (mean±SD) | 65±10 | 65±9 |

Unless indicated otherwise, results represents percentages of patients or lesions
¶ According to the American College of Cardiology/ American Heart Association lesion characteristics classification, TIMI= Thrombolysis in Myocardial Infarction grade flow.
NOTE: Except for lesion length (p=0.02), there were no statistical differences between groups. This was also the case when baseline characteristics were compared for direct stenting versus predilatation per operator group.

### Baseline characteristics

The baseline characteristics of patients in the two operator groups are described in Table I. There were no differences in demographics and clinical characteristics between both operator groups. Also lesion characteristics did not differ except for lesion length in favor of the lower-volume operator group (8.8 vs. 9.8 mm, p=0.02). The proportion of direct

stented randomized patients was similar to that of predilated patients in both operator groups. In addition, no statistical differences in baseline characteristics existed between both treatment strategies per operator group.

Table II: Procedural results in patients with lesions treated by high-volume versus lower-volume operators

| PROCEDURAL RESULTS | HIGH-VOLUME | LOW-VOLUME | P |
|---|---|---|---|
| Direct stenting success | 87 | 94 | 0.10 |
| Stent length, mm (mean±SD) | 15.8 | 14.7 | 0.05 |
| Stent size, mm (mean±SD) | 3.1±0.4 | 3.0±0.4 | 0.05 |
| Dissection after initial stent placement | 12 | 14 | 0.74 |
| Postdilatation | 15 | 24 | 0.06 |
| Post minimal lumen diameter, mm (mean±SD) | 2.6±0.5 | 2.6±0.5 | 0.75 |
| Platelet GP IIb/IIIa antagonist usage | 5.2 | 6.1 | 0.80 |
| Procedural success (overall) | 97 | 96 | 0.54 |
| Direct stenting | 99 | 97 | 1.00 |
| Predilatation | 95 | 94 | 1.00 |
| Procedural time, min (mean±SD) | 30.8±14.9 | 42.2±20.0 | <0.001 |
| Fluoroscopy time, min (mean±SD) | 7.5±5.4 | 11.2±8.3 | <0.001 |
| Use of contrast agent, ml (mean±SD) | 180±79 | 228±92 | <0.001 |
| Use of balloons/ patient (mean±SD) * | 0.7±0.7 | 0.8±0.8 | 0.88 |
| Use of stents/ patient (mean±SD) | 1.2±0.6 | 1.3±0.6 | 0.35 |
| Procedural costs, Euro (mean±SD) * | 1982±745 | 2164±866 | 0.05 |

Results are presented as % of patients or lesions unless stated otherwise.
GP=glycoprotein
* Number of balloons and procedural costs were significantly different in favor of direct stenting for both operator groups

### Procedural and immediate angiographic results

Table II summarizes the procedural results. Success of direct stenting did not significantly differ between both operator groups. Longer and bigger stents were used by the high-volume operators. There was a trend towards more postdilatation in the lower volume operator group (24% vs. 15%, p=0.06). Procedural success, including in-hospital MACCE, was similar between operator groups. Procedural time, fluoroscopy time, use of contrast agent and therefore procedural costs were all significantly reduced in favor of the high-volume group. Mean number of stents and balloons used per patient were similar between operator groups. Procedural success between direct stenting and stenting after predilatation per operator group was similar. For both operator groups direct stenting resulted in a reduction in the mean number of balloons used per patient and procedural costs as compared to stenting after predilatation.

### Six month clinical follow-up

Table III shows that at 185±125 days after the baseline procedure, overall cumulative MACCE had occurred more often in the lower-volume operator group (21.1% vs. 12.2%, p=0.03). Also the separate event rate of death, MI, TLR, CABG, repeat PCI

and stroke all occurred less in favor of high-volume operators although not statistically significant. Also the occurrence of angiographic restenosis was lower in patients treated by experienced operators (19.8% vs. 22.6%) although not statistically significant. When direct stenting was compared to predilatation in the lower-volume operator group there was a large difference in binary restenosis rate in disadvantage of direct stenting (31.5% vs. 14.9%, p=0.005). In the high-volume group the opposite result was the case (15.8% vs. 24.1%, p=0.20).

Table III. Cumulative six month major adverse cardiac and cerebral events and angiographic restenosis rates in patients treated by high-volume versus lower-volume operators.

| 180-DAY CLINICAL FOLLOW-UP | HIGH-VOLUME (n=115) | LOW-VOLUME (n=180) | P |
|---|---|---|---|
| MACCE (all) | 12.2% | 21.1% | 0.03 |
| Direct stenting/ Predilatation | 10.0/ 14.5 | 20.5/ 21.7 | |
| Death (all) | 0 | 1.1% | 0.52 |
| Direct stenting/ Predilatation | | 2.3/ 0 | |
| Myocardial infarction (all) | 0.9% | 5.0% | 0.15 |
| Direct stenting/ Predilatation | 1.7/ 0 | 3.4/ 6.5 | |
| Target lesion revascularization (all) | 6.1% | 10.0% | 0.29 |
| Direct stenting/ Predilatation | 3.3/ 9.1 | 9.1/ 10.9 | |
| CABG (all) | 1.7% | 3.9% | 0.49 |
| Direct stenting/ Predilatation | 1.7/ 1.8 | 4.5/ 3.3 | |
| Repeat PCI (all) | 10.4% | 15.4% | 0.29 |
| Direct stenting/ Predilatation | 8.3/ 12.7 | 14.8/ 15.2 | |
| Stroke (all) | 0 | 0.6% | 1.00 |
| Direct stenting/ Predilatation | | 1.1/ 0 | |
| ANGIOGRAPHIC BINARY RESTENOSIS (all) | 19.8% | 22.6% | 0.66 |
| Direct stenting/ Predilatation | 15.8*/ 24.1 | 31.5*/ 14.9** | |

Results are presented as % of patients (MACCE) or lesions (binary restenosis).
MACCE = Major Adverse Cardiac and cerebral Events, CABG = Coronary artery Bypass Grafting, PCI = Percutaneous Coronary Intervention.
* Chi-square test (p = 0.01) comparing restenosis rate after direct stenting between the two operator groups.
** Chi-square test (p = 0.005) comparing restenosis rate after direct stenting versus predilatation within lower-volume operator group.

Results in overall MACCE favored direct stenting in the high-volume group and was equal to predilatation in the lower-volume group. Individual endpoints such as death, MI, TLR, CABG, Repeat PCI and stroke were not significantly different between treatment strategies for both operator groups.

## Discussion

This study is the first to investigate the impact of operator volume on early and long-term outcome after direct stent implantation versus stenting after predilatation. It compared high-volume with lower-volume operators treating selected patients with stable or unstable angina pectoris.
This study shows that high-volume compared to lower-volume operators have shorter and modestly cheaper procedures, shorter radiation times, lower contrast usage and most importantly, a 50% reduction in occurrence of MACCE at six month. Clinical and angiographic outcome after direct stenting compared to stenting after predilatation seems to be positively influenced by high-volume operators, although no statistical difference was reached. Particularly noteworthy is that direct stenting compared to stenting after predilatation resulted in significantly higher restenosis rates in the lower-volume operator group.
There is a trend towards more difficult patients at baseline for the high-volume operators. Because lesions were approximately 1mm longer in the high-volume group, these operators used 1 mm longer stents. Although baseline reference diameter was similar between the two operator groups, high volume operators used larger diameter stents. One possible explanation for reduced restenosis and MACCE rates at six month in the high-volume group could be that experienced operators choose more often for the concept `the bigger is better` [32]. Other explanations are that more experienced operators have shorter procedures and radiation times, less postdilatation and master better the technique of direct stenting. The more demanding aspect of this technique is decreased visualization due to reduced distal contrast run-off which could lead to imprecise positioning and, hence, difficulties in sizing stent diameter and length. Moreover, lower-volume operators seem to affect the vessel wall more often when using this technique, as there existed a significant difference between direct stenting and stenting after predilatation regarding restenosis rates.

### Comparison to literature

Our findings on (direct) stenting regarding the relationship between volume and outcome are in line with results of previous studies on PCI and surgery, except for one investigation.
This exception is presented by Malenka et al.[33] on the relationship between operator volume and outcomes after PCI in five high-volume centers (>600 procedures/ year). Operators were divided into three groups: lower-volume (mean 68 cases/yr.), middle volume (mean 119 cases/yr.) and high volume (mean 209 cases/yr.). Using adjusted rates for clinical success, in-hospital mortality, MI and CABG as the outcomes of interest, the authors concluded that there is no difference between operator volume and outcomes. However, Edward Hannan [34] showed in an editorial comment that such a conclusion is an oversimplification of the findings.
On the other hand, McGrath et al. [35] showed that Medicare patients treated in the year 1997 by higher volume operators (>60 procedures) experienced better outcomes

after PCI compared to lower-volume operators (<30 procedures). After adjustment for case mix, patients treated by these lower-volume operators had an increased risk of CABG (2.25% vs. 1.55%; P<0.001), but no difference in 30-day mortality rate (3.25% vs. 3.39%; p=0.27). Several other studies also showed an inverse relationship between operator volume and outcome [36-38].

Study design and limitations

The findings of our study holds for patients selected for the direct stenting technique, i.e. (un)stable angina pectoris, native single vessel lesion PCI, no densely calcified lesions, no severe tortuosity or lesion at an ostium or bifurcation lesions. We are unable to comment on the overall PCI population regarding a relationship between operator volume and outcome.

Relatively low patient numbers were used, especially in the high-volume group. It could have been possible that the trend towards lower restenosis rates in favor of high-volume operators would have reached statistical significance. Noteworthy is that in such a modest group cumulative MACCE in the high-volume group already differed statistically significantly from the lower-volume group making our results more amendable.

Operators were unaware that their performance was evaluated. Furthermore, all endpoint information was collected by an independent research doctor minimizing information bias of operators on outcome. Information for MACCE follow-up was 100% complete.

We are aware of the fact that the relatively arbitrary selection criteria for high and lower-volume operators could have led to an overestimation of the differences in outcome between operator groups. However, our lower-volume physicians were well-trained fellows with a minimum caseload of at least 75 and under supervision of interventional cardiologists. Nevertheless, our high-volume physicians had been performing PCI-procedures since its introduction. It can be hypothesized that clinical outcome would have been worse in the lower volume operator group in case interventions had been performed in low-volume clinics without experienced supervision. One should take this into account when translating our results to general practice.

Another issue is that our findings are based on a prospective subgroup analysis, which may limit the level of evidence presented. Adequate controls would have needed randomization because of variation in the distribution of both observed and unobserved confounders. However, performance of a prospective randomized trial to determine the influence of operator volume might raise ethical and logistic tribulations.

Practical notes

Our findings support the ACC guidelines which suggest to maintain proficiency in coronary interventions by more than 75 procedures/ year. The direct stenting technique should preferably be restricted, only to operators with several years of experience regarding restenosis rates. This study further indicates that prolonged training periods for fellows, and even more, intensive supervision by experienced operators is mandatory.

It should be made clear that our findings cannot be extended to operators working in lower volume clinics or to moderate volume operators. In addition, one must bear in mind that even when operator volumes are significantly related to patient outcome, exceptions will be present, i.e. low volume operators with good outcomes and high volume operators with poor outcomes. Individual operator performance should be assessed as volume alone does not appear sufficient to assure appropriate PCI outcomes [39].

## Conclusion

In patients selected for the direct stenting technique, high and lower volume operators experience similar procedural success rates following stent implantation. However, cases performed by high-volume operators resulted in significantly faster procedures, less radiation time, lower contrast usage, lower need for postdilatation, modestly lower procedural costs and most importantly a 50% reduction in MACCE as compared to the lower-volume physicians. For the lower-volume group there were significantly higher restenosis rates after direct stenting compared to stenting after predilatation. Our findings indicate that operator volume is an important determinant for patient outcome. The technique of direct stenting should be reserved for operators with several years of experience at sufficient volume. This study further implicates that prolonged training periods for fellows and even more intensive supervision by experienced operators seem mandatory.

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# Complete versus Culprit Vessel Percutaneous Coronary Intervention in Multivessel Disease: A randomized Comparison.

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## ABSTRACT

Study objectives To compare the safety, efficacy and costs of complete versus `culprit` vessel revascularization in multivessel coronary disease treated with percutaneous coronary interventions (PCI).

Patient population and methods This trial enrolled 219 patients with multivessel coronary artery disease amenable to PCI and an identified culprit vessel. They were randomized to revascularization of all lesions (complete revascularization group, n=108) versus revascularization limited to the culprit vessel (culprit vessel group, n=111). The primary endpoint of the trial was a composite of major adverse cardiac events (MACE), including cardiac or non-cardiac death, myocardial infarction, need for coronary artery bypass graft surgery, and repeat PCI up to one year.

Results: Procedural success was higher in the culprit vessel than in the complete revascularization group (93.7 vs. 81.5%, P=0.007). MACE rates at 24 h, one month and one year were similar in both groups. At a mean follow-up of 4.6 ±1.2 year, overall MACE rates were 40.4% versus 34.6% in the culprit vessel versus complete revascularization group (NS). Repeat PCI were performed more often in the culprit vessel group (31.2 vs. 21.2%, P=0.06), for initially untreated lesions in 68% of cases. A lower consumption of medical material (e.g. stents 0.8 ± 0.9 vs. 1.3 ± 1.3, P <0.001) was associated with lower procedural costs in favor of the culprit vessel group (Euros 5784 vs. 7315, P <0.001). However, at one year and to the end of follow-up, costs had equalized in both groups.

Conclusions: Complete versus culprit vessel revascularization in multivessel coronary disease treated with PCI was associated with a lower procedural success rate, similar overall MACE rates and initially higher costs. However, on the long-term, costs equalized in both treatment groups, as fewer repeat PCI were needed in the complete revascularization group. Whether to perform culprit vessel versus complete revascularization remains a case-by-case decision.

## Introduction

Percutaneous coronary interventions (PCI) have become increasingly important in the treatment of patients with stable or unstable angina pectoris due to occlusive coronary artery disease (1). In most interventional cardiology centers, PCI is usually limited to the vessel responsible for ischemia (culprit vessel), identified by evolutionary electrocardiographic changes, scintigraphic or echocardiographic information, or by a positive post-infarction stress test. In addition, left ventricular and coronary angiographic findings assist in the identification of the culprit vessel.
In patients with multivessel disease, significant lesions are present in coronary arteries other than the culprit vessel. Whether more than one vessel is ultimately treated depends on the operator, stenoses characteristics, amount of myocardium at risk, and on the angiographic outcome after treatment of the culprit vessel. Retrospective analyses have suggested that the long-term prognosis is favorably influenced by more complete revascularization (2-4), which may obviate later coronary artery bypass grafting (CABG) or PCI of the lesions initially left untreated. On the other hand, it has been argued that systematic attempts at complete percutaneous coronary revascularization is associated with longer procedures, higher rates of periprocedural complications, greater material consumption and procedural costs, more hospital admissions, and a higher risk of restenosis, although the latter should be limited by the growing use of stents (2-33). Whether patients with multivessel coronary artery disease who are eligible for PCI should undergo culprit vessel versus all vessel revascularization has not been settled by the results of a properly randomized study comparing the outcomes, complications and need for repeat revascularization associated with these two strategies. Therefore, this prospective randomized trial was conducted to compare the results of PCI limited to the culprit vessel with PCI of all vessels with ≥ 50% stenoses. The initial results, clinical outcomes and costs up to five year after the baseline procedure are presented.

## Methods

### Selection of patients

Participants were recruited among all patients admitted to the Amsterdam Department for Interventional Cardiology, a large, regional tertiary center. The Medical Ethics Committee of our hospital approved the study and written informed consent was obtained from all patients. Patients of all ages were eligible for the trial if they had ≥ 50% stenoses of ≥ 2 native epicardial vessels ≥ 2.0 mm in diameter, supplying separate myocardial territories. All stenoses had to be suitable for PCI, and the culprit vessel was to have been identified by two independent, expert interventional cardiologists on the basis of additional clinical information, including electrocardiography, echocardiography, scintigraphy or coronary angiography.
Major exclusion criteria were PCI during acute myocardial infarction, comorbidity limiting the life expectancy to < 1 year, stenosis of a venous or arterial bypass graft, or

participation in another clinical trial. Patients suspected of non compliance or living at great distances were also excluded from the study.

### Randomization scheme

Patients were prospectively randomized to undergo PCI of either the coronary artery thought to be responsible for ischemia (culprit vessel), or of all ≥ 50% stenoses (complete revascularization). Randomization to treatment was performed by a computerized allocation algorithm, yielding 111 patients assigned to culprit vessel and 108 to complete revascularization.

### Percutaneous coronary interventions

The choice of percutaneous revascularization technique, including balloon, perfusion balloon, cutting balloon, rotablator, directional atherectomy or stents, whether planned or not, was left to the discretion of five interventional cardiologists. In patients randomized to complete revascularization the goal was to perform PCI of all stenoses in a single procedure. If, for any reason, a staged procedure was necessary, the second procedure was planned within 30 days. The procedures were routinely performed by radial artery puncture, unless contraindicated.

### Antithrombotic regimen

Aspirin, 500 mg, was administered to all patients immediately before the procedure. An initial bolus of 10.000 U of heparin was given intravenously, followed by additional 5000 U hourly boluses throughout the procedure. Overnight continuation of a heparin infusion, and the postoperative use of platelet glycoprotein IIb/IIIa inhibitors were left to the operator's discretion. After stent implantation, 500 mg of ticlopidin was administered immediately following the procedure and continued in a dose of 250 mg/day for one month. Aspirin, 100 mg/day, was continued for at least six month in all patients.

### Endpoint definitions

The primary endpoint of the trial was a composite of major adverse cardiac events (MACE), including cardiac or non-cardiac death, myocardial infarction (MI), need for CABG, and repeat PCI up to one year. Secondary endpoints included MACE, rates of additional PCI, incidence of recurrent angina pectoris according to the Canadian Cardiovascular Society classification (CCS), and medical costs immediately after the procedure, at one month, and at five years.
Procedural success was defined as the achievement of an angiographic residual stenosis < 30% and a TIMI grade III flow after treatment of all lesions, and the occurrence of no adverse in-hospital clinical event. (34)
The diagnosis of MI was based on prolonged chest pain associated with either new > 0.03 s Q waves on surface electrocardiogram, or a rise in creatine kinase enzyme above 200 U/L, or in the MB fraction above 20 U/L. Serial enzymes were measured, or electrocardiograms recorded only in the presence of signs or symptoms consistent with a myocardial ischemic event. Angina pectoris was graded as CCS class I, II, III or IV.

Clinical follow-up

Follow-up data including electrocardiograms, CCS class of angina pectoris, use of anti-anginal medication, MACE and date and cause of death, were recorded at 30 days, one year and five year after the baseline PCI. These data were obtained at scheduled follow-up visits or, if necessary, by review of medical records or by telephone interviews. Though the study design did not allow blinding of the interventional cardiologist performing the PCI, the independent observer who collected the follow-up data was blinded to the treatment allocation.

Cost analysis

Materials, such as guiding catheters, balloons and stents used during the procedure were counted. Baseline procedural costs were estimated by preset local insurance costs (PCI = Euros 5000, Stent = Euros 1000). Additional event and hospital stay costs up to five year were estimated by multiplying events with preset local insurance costs (repeat PCI = Euros 5000, CABG= Euros 12000, coronary angiography = Euros 803, Q-wave MI= Euros 3000, 1 day in hospital = Euros 769).

Statistical analysis

A sample size of 219 patients was expected to detect a minimum treatment difference of 19% in the primary endpoint at one year, with an 80% power and a two-sided significance level set at 0.05. Endpoints were analyzed according to the "intention to treat" principle. Overall rates of MACE are presented in cumulative and rank ordered fashion.

The clinical characteristics of the population are presented as means ± standard deviation (SD), or as medians for variables with skewed distribution, or as percentages. For between-groups comparisons of non-paired continuous variables, the unpaired Student's t-test was used, or the Mann-Whitney U-test in case of skewed data distribution. Categorical variables or MACE in both groups were compared by Chi-square test. Spearman rank correlation testing (coefficient Rs) was performed to identify variables related to the primary endpoint of this study. Among the variables identified, step-down logistic regression was performed until all remaining variables were significant, to identify predictors of MACE at one year. (35) Ninety-five percent confidence intervals (95% CI) were calculated for odds ratios. The Kaplan-Meier life-table method was used to analyze time to clinical events. Comparisons of the event-free survival curves in the two treatment groups were made by Wilcoxon and log-rank test at five year of follow up. All P values are two-sided, and P values $< 0.05$ were considered statistically significant.

## Results

Table I. Baseline demographics, risk factors and coronary lesion characteristics of patients treated by culprit vessel (CVR) versus complete (CR) revascularization

| Characteristic | CVR (n=111) | CR (n=108) | All patients (n=219) |
|---|---|---|---|
| Age, y (mean±SD) | 61.7 ±10.4 | 62.0 ±9.7 | 61.9±10.1 |
| Number of all lesions | 271 | 248 | 519 |
| Number of lesions treated | 111 | 220 | 331 |
| | % of patients | % of patients | % of patients |
| Men/Women | 74/26 | 76/24 | 75/25 |
| Diabetics/dyslipedemia | 17/45 | 11/56 | 14/50 |
| Current smoking/high bloodpressure | 32/37 | 31/32 | 32/34 |
| Previous MI/CABG/angioplasty | 44/0/13 | 41/0/15 | 42/0/14 |
| Angina Pectoris CCS class I/II/III/IV | 5/19/43/33 | 6/12/40/42 | 5/15/41/37 |
| Medication | | | |
| Anticoagulation/aspirin | 7/89 | 8/90 | 7/89 |
| Nitrates/ß-blockers/calcium antagonist | 69/84/57 | 76/77/61 | 72/80/59 |
| Diuretics/ACE-inhibitor | 6/21 | 5/15 | 6/19 |
| Triple vessel disease | 9 | 3 | 6 |
| Location of culprit vessel | | | |
| Left anterior descending artery | 41 | 48 | 44 |
| Circumflex artery | 24 | 23 | 24 |
| Right coronary artery | 34 | 29 | 31 |
| Location of non-culprit vessel | | | |
| Left anterior descending artery | 43 | 29 | 36 |
| Circumflex artery | 40 | 42 | 41 |
| Right coronary artery | 29 | 29 | 29 |
| Preprocedural TIMI grade flow | | | |
| 0/I/II/III | 2/2/6/90 | 4/2/7/87 | 3/2/7/88 |
| ACC/AHA lesion classification type B2/C | | | |
| Culprit lesion/non-culprit lesion | 33/9 | 40/17 | 36/13 |

Except where indicated otherwise, all values are percentages of patients
MI = Myocardial Infarction, CABG = Coronary Artery Bypass Grafting, CCS = Canadian Cardiovascular Society, TIMI= Thrombolysis In Myocardial Infarction, ACC/ AHA = American College of Cardiology/ American Heart Association

### Baseline demographics and lesion characteristics

This single center trial enrolled 219 eligible patients among 4468 PCIs performed between August 1995 and December 1998. Their mean age at the time of baseline PCI was 62 years (range 34-85). They were clinically followed until April 2002.
Risk factors for cardiovascular disease and related medical history were evenly distributed between the two groups (table I). Trends toward a higher prevalence of diabetes and triple vessel disease in the culprit vessel group, and toward a higher prevalence of dyslipidemia in the complete revascularization group were noted, though

the differences did not reach statistical significance. In the majority of patients the culprit lesion was of type B of the American College of Cardiology/American Heart Association classification, and was located in the left anterior descending coronary artery.

Table II. Procedural success and major adverse cardiac events up to one year in patients treated by culprit vessel (CVR) versus complete (CR) revascularization.

| Procedural results and MACE | CVR (n=111) | CR (n=108) | P |
|---|---|---|---|
| Procedural success | 93.7 (104) | 81.5 (88) | 0.007 |
| Overall MACE (<24h) | 6.3 (7) | 7.4 (8) | 0.79 |
| All-cause mortality | 0 | 0 | - |
| Acute MI | 1.8 (2) | 3.7 (4) | 0.44 |
| CABG | 1.8 (2) | 3.7 (4) | 0.44 |
| Repeat PCI (<24h) | 2.7 (3) | 1.9 (2) | 1.00 |
| Overall MACE (30 days) | 14.4 (16) | 9.3 (10) | 0.30 |
| Cardiac death | 0 | 0 | 1.00 |
| Non-cardiac death | 0.9 (1) | 0 | 1.00 |
| MI | 2.7 (3) | 3.7 (4) | 0.72 |
| CABG | 1.8 (2) | 3.7 (4) | 0.44 |
| Repeat PCI | 9.0 (10) | 3.7 (4) | 0.16 |
| Overall MACE (1 year) | 32.4 (36) | 26.9 (29) | 0.37 |
| Cardiac death | 0 | 1.9 (2) | 0.50 |
| Non-cardiac death | 1.8 (2) | 1.9 (2) | 1.00 |
| MI | 5.4 (6) | 7.4 (8) | 0.59 |
| CABG | 8.1 (9) | 8.3 (9) | 1.00 |
| Repeat PCI | 23.4 (26) | 15.7 (17) | 0.17 |

Unless stated otherwise, results are presented as percentages (number) of patients.
MACE = cumulative and rank ordered Major Adverse Cardiac Events.
MI = Myocardial Infarction, CABG = Coronary Artery Bypass Grafting, PCI = percutaneous coronary intervention

### Procedural success and early complications

All randomized patients underwent an attempt at PCI. The procedural success was higher in patients randomized to culprit vessel than to complete revascularization (table II). In the former group the guidewire could not cross the stenosis in two patients, and another patient suffered from a dissection and underwent emergency CABG. In the complete revascularization group treatment of the culprit lesion was unsuccessful in eight patients, due to coronary embolization in one, dissection in three and failure to cross the guidewire through the stenosis in four patients. One patient with a dissection also developed ventricular fibrillation and another a thrombus. Both underwent emergency CABG.

Table III. Long-term (4.6±1.2 year) clinical follow-up in 109 of 111 patients (98%) who underwent culprit vessel (CVR), versus 104 of 108 (96%) patients who underwent complete (CR) revascularization.

| Long-term clinical follow-up | CVR (n=109) | CR (n=104) | P |
|---|---|---|---|
| Days in hospital since baseline procedure | 6.3±24.7 | 8.1±11.3 | 0.50 |
| Number of angiographic procedures | 0.46±0.86 | 0.40±0.77 | 0.58 |
| | % of patients | % of patients | |
| Angina Pectoris CCS class I/II/III/IV | 89/6/4/1 | 83/16/1/0 | - |
| Current medication | | | |
| Anticoagulation/Aspirin | 8/91 | 10/87 | - |
| Nitrates/ß-blockers/Calcium antagonists | 25/69/29 | 19/66/28 | - |
| Statin/ACE inhibitor | 23/66 | 30/66 | - |
| Overall long-term MACE | 40.4 (44) | 34.6 (36) | 0.40 |
| Cardiac death | 0.9 (1) | 3.8 (4) | 0.21 |
| Non-cardiac death | 1.8 (2) | 3.8 (4) | 0.44 |
| MI | 7.3 (8) | 10.6 (11) | 0.48 |
| CABG | 11.0 (12) | 9.6 (10) | 0.82 |
| Repeat PCI | 31.2 (34) | 21.2 (22) | 0.06 |
| Repeat PCI for initially untreated lesion* | 21.1 (23) | - | - |
| Target lesion revascularization | 12.0 (13) | 17.3 (18) | 0.33 |
| In-stent restenosis per stented patient** | 7.0 (4) | 17.8 (13) | 0.11 |
| Number of all revascularizations*** | | | |
| 0 revascularizations | 66.1 (72) | 74.0 (77) | 0.23 |
| 1 revascularization | 18.3 (20) | 20.2 (21) | 0.86 |
| More than 1 revascularizations | 15.6 (17) | 8.7 (9) | 0.09 |

Results indicate mean±SD or percentages (numbers) of patients.
CCS = Canadian Cardiovascular Society. PCI = Percutaneous Coronary Intervention. MI = Myocardial Infarction, CABG = Coronary Artery Bypass Grafting
* Repeat PCI of significant though protocol mandated initially untreated lesions of patients randomized to culprit revascularization.
** Number of stented patients were 57 and 73 for the culprit and complete group, respectively.
*** Revascularizations include all repeat PCI and coronary surgery after the baseline procedure.

In the completely revascularized group, treatment of the second and third lesion, i.e. non-culprit lesions, was unsuccessful in eight patients. In 5 patients, the guidewire could not be advanced through the stenosis and 3 patients suffered from occlusive dissection. The acute vessel closure was uncomplicated in one patient, another patient suffered from a non-fatal MI, and the third patient underwent emergency CABG. Rates of MACE within the first 24 h did not differ significantly between the two treatment groups. There was no periprocedural death. One patient randomized to culprit vessel revascularization died 21 days after successful PCI with stent placement in the right coronary artery. The cause of death was respiratory failure due to rapidly progressive lung cancer. At autopsy, patency of the right coronary stent was confirmed.
At 30 days there was a trend toward a higher MACE rate after culprit vessel revascularization, due to an over two-fold higher rate of further PCI (9%) than in the complete revascularization group (4%). This difference was attributable to six patients

who underwent PCI of an initially untreated non-culprit vessel, because of persistent or recurrent symptoms after successful revascularization of the culprit vessel. A slightly higher percentage of patients in the culprit vessel group (19%) reported angina pectoris at 30 days than in the complete revascularization group (13%) though the difference was not statistically significantly. The use of anti-anginal medications was similar in both groups.

One-year clinical follow-up

A one-year follow-up was available in all patients. At that time, the incidence of death, MI and CABG were similar between the two groups (table II). The 1-year rate of MACE, the primary endpoint of this trial, did not differ statistically, though was slightly higher in the culprit vessel (32.4%) than in the completely revascularized group (26.9%). This difference was mainly attributable to a trend toward a higher rate of repeat PCI in the culprit group (23.4%) than in the complete revascularization group (15.7%). In multivariate analysis, among 15 demographic, clinical and angiographic variables tested, diabetes mellitus was an independent predictor of 1-year MACE (odds ratio: 2.6, 95% CI 1.2-5.6, P=0.016). Treatment assignment was not a predictor of MACE.

Long-term clinical follow-up

Table III presents the results available in 97% of the overall cohort at 4.6±1.2 years of follow up. The mean number of hospital days spent, or of diagnostic coronary angiographic procedures performed, between the baseline PCI and the last follow-up were similar in the two treatment groups. Furthermore, a ≥ 2 CCS angina pectoris classes increase between baseline and the last follow-up was measured in 80% of patients in both groups, and the consumption of medications at last follow-up was similar with both treatment strategies.

Rates of cardiac death and MI did not differ statistically between groups. The proportions of patients free from coronary revascularization after the baseline procedure were 66.1% in the culprit vessel and 73.1% in the complete revascularization group (NS). However, the rate of further PCI was higher in the culprit vessel group, causing a trend toward a higher MACE rate in this group (40.4% vs. 34.6%). There was also a trend toward > 1 revascularization procedure/patient in the culprit vessel group. PCI for an initially untreated lesion were performed in 21.1% of patients randomized to the culprit vessel group. In-stent restenosis per stented patient tended to occur more often in the complete revascularization group (17.6% vs. 7.0%). The Kaplan-Meier survivals free from further revascularization (repeat PCI and CABG) after the baseline procedure in each treatment group are presented in figure 1 (NS, log-rank analysis). Further revascularization was mostly performed within one year after the baseline procedure in both groups. Thereafter, the CABG and repeat PCI-free survival in the complete revascularization group remained stable, whereas it continue to decrease over the following two years in the culprit vessel group.

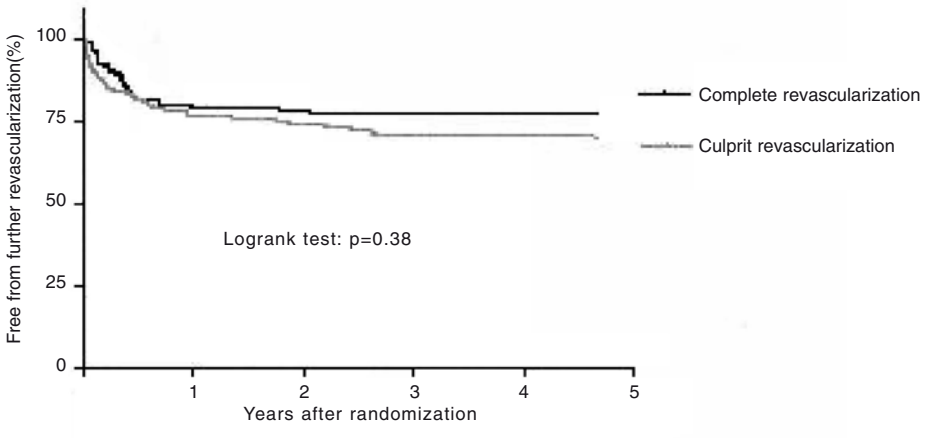


Figure 1. Kaplan-Meier survival free from coronary surgery and repeat percutaneous coronary intervention

## Material utilization and cost analysis

Table IV shows that fewer guiding catheters, balloons and stents were used during the baseline procedure in the culprit vessel than in the complete revascularization group (P <0.001). This difference in resource utilization, corresponded to a Euros 1531 lower procedural cost in the culprit vessel group (P <0.001). A significant difference of Euros 1407 persisted in favor of the culprit vessel group at one month (P=0.047). However, at one year, cost calculations had equalized between treatment groups, mostly as a result of the higher number of repeat PCI and diagnostic coronary angiographic procedures performed in the culprit vessel group. This remained unchanged to the end of follow-up.

Table IV. Comparisons of resource utilization during the baseline procedure as well as procedural and follow up costs for patients treated with culprit vessel (CVR) versus complete (CR) revascularization.

| | CVR | CR | P |
|---|---|---|---|
| RESOURCE UTILIZATION | | | |
| Guiding catheters, mean±SD (n) | 1.2±0.6 (132) | 1.8±1.0 (190) | 0.001 |
| Balloons, mean±SD (n) | 1.3±0.9 (142) | 2.1±1.1 (224) | 0.001 |
| Stents, mean±SD (n) | 0.8±0.9 (87) | 1.3±1.3 (145) | 0.001 |
| PROCEDURAL COSTS | Euros 5784±938 | Euros 7315±2490 | 0.001 |
| ONE MONTH COSTS | Euros 7786±4803 | Euros 9193±5790** | 0.047 |
| ONE YEAR COSTS | Euros 12417±12046 | Euros 12985±9533 | 0.699 |
| OVERALL LONG-TERM COSTS | Euros 14093±12012 | Euros 14548±11996 | 0.779 |

Values represent mean cost per patient ± SD in Euros or mean number of items used±SD.

## Discussion

This study was designed to address a quandary regularly encountered by interventional cardiologists, and was the first to compare prospectively and randomly the early and late clinical results, and the costs of complete percutaneous coronary versus revascularization limited to the culprit vessel.

### Main findings of the study

The procedural success rate was higher in patients randomized to culprit vessel revascularization, a difference due to more lesions treated in the complete revascularization group, thus a higher rate of lesion crossing failure. In contrast, the rate of additional revascularization at one month was at least two-fold higher after culprit vessel than after complete revascularization, because of the need to perform PCI on initially untreated lesions. Likewise, at one year, there was a trend toward a higher MACE rate in the culprit vessel group, mainly caused by a greater need for repeat PCI, a trend which persisted throughout the follow-up. Though procedural costs were lower in the culprit vessel group, this difference had disappeared by one year for the same reasons.

### Comparison with previous studies

The information published thus far relative to the long-term results of PCI in patients with multivessel disease as a function of completeness of revascularization was acquired retrospectively (4,30,36,37), except for a single small study by Kussmaul et al., who randomized 43 patients with multivessel disease to culprit vessel versus complete revascularization by PCI. (26) The article does not specify whether complete revascularization was, indeed, achieved in all patients randomized to that group. Three PCI-related complications occurred in the culprit vessel group, as opposed to none in the completely revascularized group. The authors interpreted this as chance instead of related to the chosen strategy. At six months, 16% of patients in the culprit vessel group reported recurrence of angina pectoris, compared to 42% in the completely revascularized group. There were no differences in the incidence of repeat PCI and CABG. The authors suggested that PCI limited to the culprit stenosis may be as effective as complete revascularization.

Reeder et al. analyzed the outcomes of 867 patients with multivessel disease. (4) After successful PCI, 41% of patients had no ≥70% residual stenoses (completely revascularized group) and 59% had at least one ≥70% stenoses (incompletely revascularized group). Over as follow-up of approximately two years, more CABGs were performed, more complaints of angina were reported and mortality was higher (P=0.05) in the incompletely than in the completely revascularized group. Rates of repeat PCI or myocardial infarction did not differ between groups. After correction for differences in baseline characteristics no significant difference was found between the two groups. The authors concluded that the prognosis was not determined by the extent of

revascularization but by the baseline variables. Several other studies have failed to show an advantage of one treatment strategy versus the other (2,3,7).

### Study design and limitations

In over three years, 4468 PCIs were performed in our center. Approximately 5% of the patients had multivessel disease amenable to PCI, and met our study's the inclusion/exclusion, an indication of the magnitude of this clinical problem. A larger study population recruited by multiple medical centers may have enabled the detection of subtle differences between the two treatment groups. On the other hand the single center trial design results offered more uniformity to the study.
The findings of this study cannot be directly compared with the results of trials using newer PCI methods and instrumentation. Nevertheless, even under these new conditions, it remains important to know whether to perform complete revascularization or to limit the procedure to the culprit vessel.
Randomization and consecutive enrolment minimized the selection biases by distributing the baseline characteristics evenly between the treatment groups. Although the study could not be blinded in its periprocedural phase, follow-up data, including death, MI, repeat PCI, CABG and CCS anginal class were gathered by a blinded investigator.
Patients who underwent culprit vessel revascularization only, and their primary physician, were aware of other "untreated lesions", which may have been the source of more complaints of angina and an greater need for further PCI in that group.
Furthermore a relative paucity of statin use during the first two years of the study may have contributed to the progression of untreated lesions in the culprit vessel group, perhaps increasing the number of repeat PCI in that group.
Analyses were adjusted for major confounders, which did not change the results. In our study six protocol violations occurred, i.e. six patients randomized to complete revascularization underwent in fact culprit vessel PCI only. Analyses per protocol without these violations confirmed results similar to those obtained by intention-to-treat analyses.

### Practical clinical implications

The introduction of drug eluting stents will markedly reduce the rate of in-stent restenosis and the need for further revascularization procedures. (33) The completely revascularized group would probably benefit the most from this new development, since, in that group a high percentage of repeat PCI were performed for in-stent restenosis. Since more stents were placed in that group, in-stent restenosis per patient also occurred more often. By contrast, in the culprit vessel group, repeat PCI was mainly performed for recurrent angina due to initially untreated lesions. The complete elimination of in-stent restenosis in our study would have resulted in a 38% overall long-term MACE rate in the culprit vessel versus 22% in the complete revascularization group. Further multicenter randomized trials using this new stent technology will be needed to corroborate the putative ability of complete revascularization to reduce the long-term need for repeat PCI and, perhaps, the overall MACE rates and costs

of treatment. At present, however no clear advantage has been shown of one treatment strategy versus the other. Therefore, the decision to perform a complete revascularization, or to limit the procedure to the culprit vessel in patients with multivessel disease remains a decision to be made by individual operators and patients.

## Conclusions

In multivessel coronary disease, complete revascularization by PCI was associated with a lower procedural success rate, higher procedural costs and similar in-hospital and one year MACE rates. However, on the long-term, more repeat PCIs were conducted in patients treated by culprit revascularization only, mostly because of the need to treat lesions initially left untreated. As a consequence, incremental costs had equalized within one year. The findings of this study indicate that the decision to perform culprit vessel versus complete revascularization by PCI in patients with multivessel coronary artery disease remains a decision to be made on a case-by-case basis.

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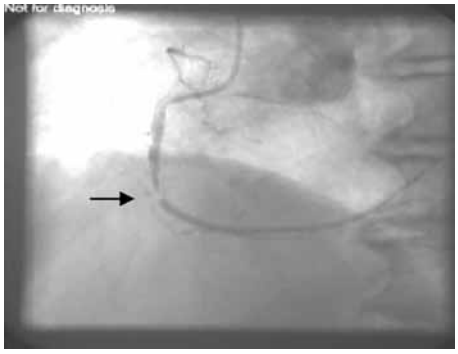
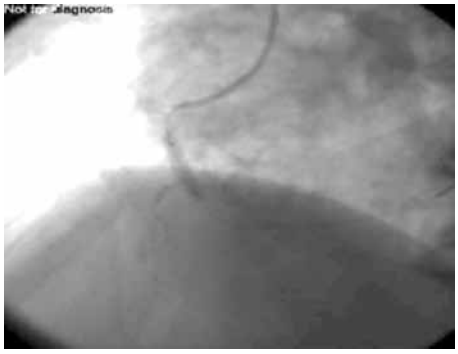
1 2 3 4 5 6 7 8 9 10

# Case reports on direct stenting

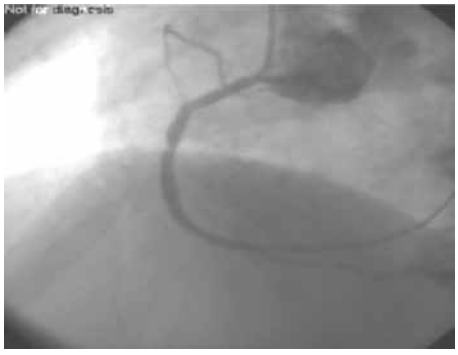
## Case 1: Direct stenting & Deep intubation into the right coronary artery



History: This 76 year old male patient was admitted with unstable angina pectoris and elevated troponin.
Angiography: Normal LV function. Single vessel disease with an eccentric and tight stenosis in segment 2 of the right coronary artery (arrow).
Policy: Transradial direct stenting via 5F guide.
Stent size: 3.5/14mm

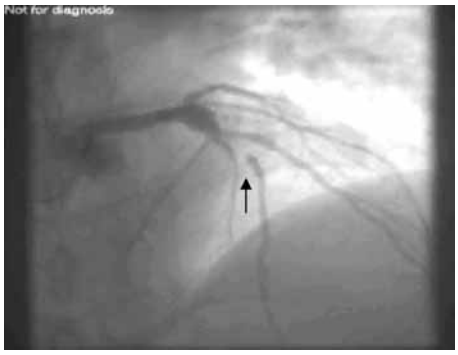


Procedure: Percutaneous coronary intervention was performed via the right radial artery. Over the stent catheter, the guide could be advanced into the right coronary artery. The stent could cross the tight lesion without any backup problems.

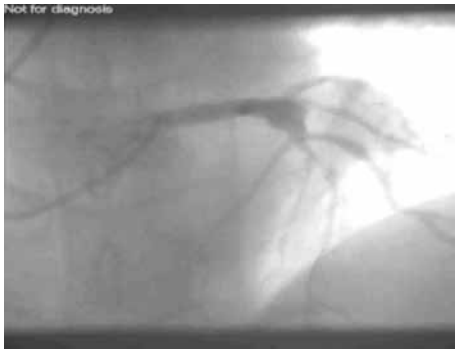


Result: The result of direct stent implantation was good in multiple views. A minor step up could be seen without signs of dissection.
Clinical course: The patient was discharged the evening of the procedure.
30 days follow-up: Uneventful
Comments: Deep intubation of 5F guides becomes routine treatment to achieve excellent support. This maneuver is safe as long as the guide is advanced over a balloon or stent catheter.

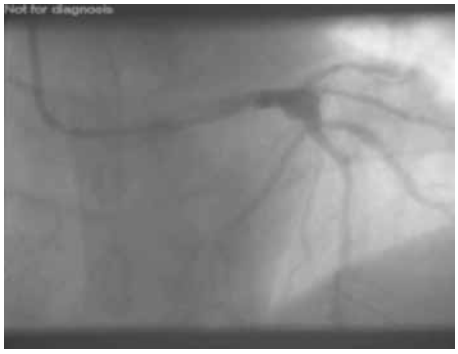
## Case 2: failed direct stenting in large side branch




History: A 58-year-old male patient was admitted with stable angina pectoris class II and a positive exercise test.
Angiography: Normal LV function. Single vessel disease with a lesion in the left anterior descending artery (arrow), just distal to a large diagonal. The diagonal had no ostial disease.
Policy: Transradial direct stenting via 5F guide.
Guide: 5F, Judkins Left4 later 6F kimny
Stent size: 2.5/14mm

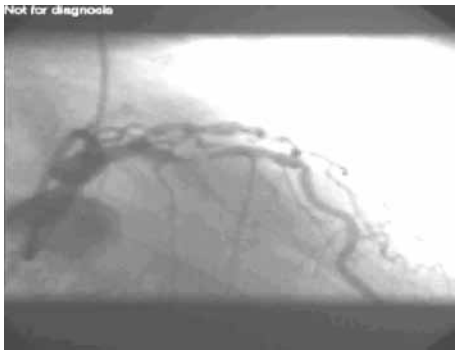



Procedure: Angioplasty was performed via the right radial artery. The stent could not be advanced over the lesion. The guide was changed for a 6F kimny and the lesion was predilated with a 2.5 balloon. After this, the stent could be successfully placed. The diagonal was not protected because the ostium was without disease.

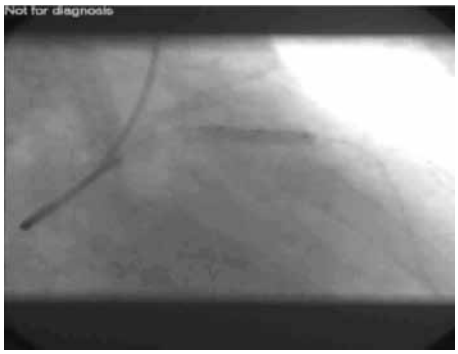



Result: The result of stent implantation was good. The diagonal was not compromized by the stent placement.
Clinical course: The patient was discharged the evening of the procedure.
30 days follow-up: Uneventful
Comments: Sometimes, direct stenting fails, even in simple lesions. This can be due to poor guide support, in combination with a hard, calcified lesion, which is not always anticipated on the coronary angiogram. One might replace the guide to improve support and predilate. New crimping techniques for securement of the stent on the balloon decrease the risk of stent loss. Secondly, when a larger sidebranch is involved in the stented segment and the ostium is free of disease, the stent can be placed without protecting the sidebranch. If the ostium is diseased a protecting guidewire should be placed. No kissing techniques can be performed via 5F guides.

## Case 3: Ultra fast direct stent procedure



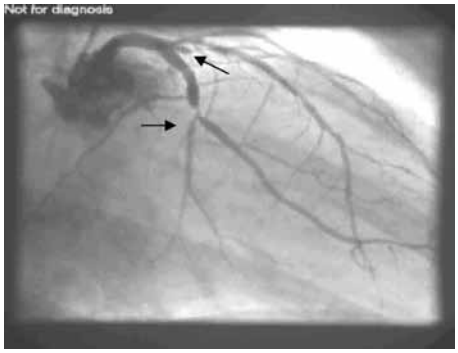

History: This 79-year-old female patient was admitted with unstable angina pectoris and electrocardigraphic changes in the anterior leads.
Angiography: Normal LV function. One vessel disease with an eccentric lesion in the proximal left anterior descending artery
Policy: Transradial direct stenting via 5F guide
Guide: 5F;JL4
Stent size: 3.5/14mm



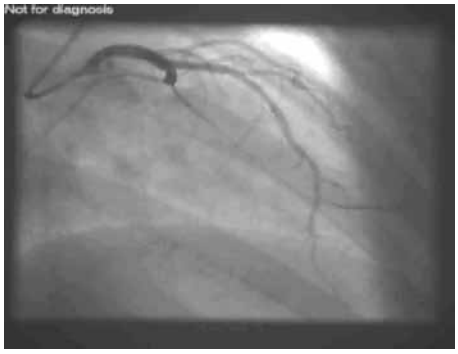

Procedure: Percutaneous coronary intervention was performed via the right radial artery. No problems were encountered during placement of the stent in this eccentric lesion.


Result: The result of stent implantation was perfect in both views.
Clinical course: The patient was discharged the evening of the procedure
30 days f.up: uneventful
Comments: The whole procedure took 15 minutes with 4 minutes of fluoroscopy time. This adds to the patients comfort, reduced ischemia time and reduced cardiac complications.

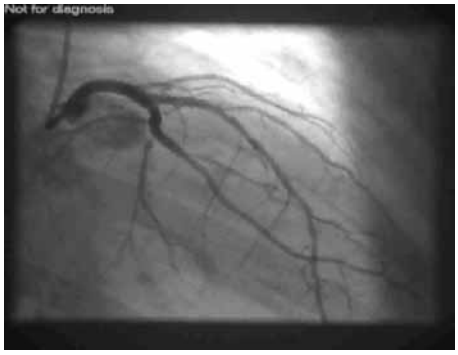
## Case 4: Multivessel direct stenting




History: This 59-year-old female patient was admitted with stable angina pectoris class III in spite of maximal medication.
Angiography: Normal LV function. Two vessel disease with a lesion in the left anterior descending artery and circumflex artery (arrows).
Policy: Transradial direct stenting via 5F guide.
Guide: 5F;JL4
Stent size: 3.0/14mm (2x)

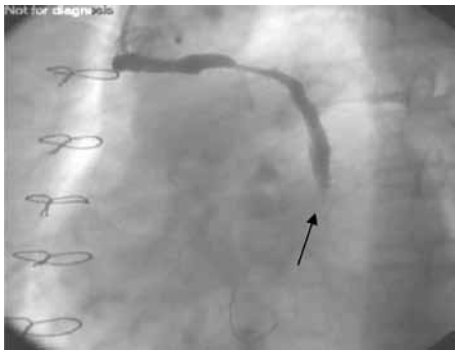



Procedure: Percutaneous coronary intervention was performed via the right radial artery. First the left anterior descending artery was treated without problems. Direct stenting was also performed successfully at the circumflex lesion. The stent easily crossed the lesion despite the severe degree, the circumflex location and the (mild) curve just proximal to the lesion.

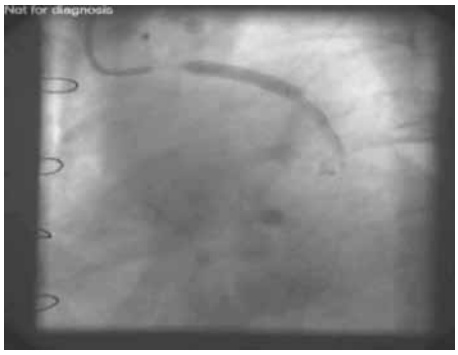



Result: The result of stent implantation was perfect in both views
Clinical course: The patient was discharged the evening of the procedure
30 days f.up: Uneventful
Comments: The whole procedure took 20 minutes. Combined with the transradial approach high turn-overs can be achieved in interventional labs.

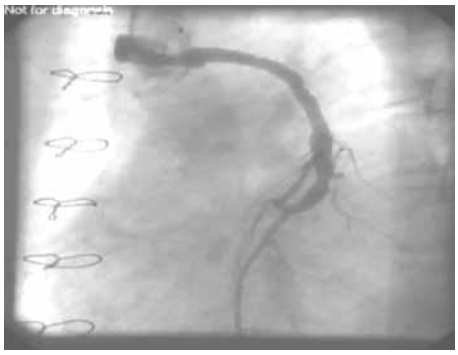
## Case 5: direct stenting in saphenous vein graft lesion




History: A 67-year-old male patient was admitted with class III angina pectoris. The patient underwent coronary artery bypass grafting two times.
Angiography: Moderate LV function. Triple vessel disease. The target vessel was the graft to the left anterior descending artery (arrow).
Policy: Transradial direct stenting
Guide; 5F; JR4
Stent size: 4.0/18mm




Procedure: The large stent easily crossed the 5F guide and the tight stenosis. After placement flow was temporarily decreased. After nitroglycerin and adenosin TIMI grade III flow was achieved.




Result: The result of stent implantation was good.
Clinical course: the patient was discharged the next morning.
30 days f.up; Uneventful
Comments: Percutaneous coronary intervention of old saphenous vein grafts carry the risk of distal embolization. So intravascular manipulations should be kept to a minimum. It is conceivable that stenting after predilatation may cause embolization of debris, which may be prevented by direct stenting. At present current stents and/ or distal protection devices are available for this indication.

## Summary

This thesis compares two new treatment strategies in intervention cardiology with their respective alternative approaches. The first is direct stenting, i.e. stenting without predilatation compared to predilatation followed by stent placement. The second is complete revascularization in multivessel disease with PCI versus treatment of the culprit vessel only, i.e. vessel thought to be responsible for ischemia,

Direct coronary stenting compared to stenting after predilatation in selected patients with stable or unstable angina pectoris:
Now that stent implantation is commonly an elective procedure, predilatation is only an intermediate step to ensure safe passage across the stenosis and full expansion of the stent. With advances in stent design and stent delivery systems a new strategy of direct stenting has been developed. Several studies reported that direct stenting is less costly, saves procedural time and offers the hypothetical advantage of causing less vessel wall injury by facilitating reendothelialization, which may result in decreased restenosis rates. However, the direct and forceful implantation of the stent through the stenosis may be considerably more traumatic than its insertion after balloon predilatation.

Chapter two includes a literature review to investigate these opposing effects of direct stenting. Its objective was to review the current available data from studies assessing feasibility, safety, clinical outcome and cost-effectiveness of direct stenting. In appropriate selected lesions direct stenting proved to be safe, feasible and an effective method for treating coronary artery disease. It has a low rate of final procedural failure and complications similar to stenting after predilatation.
Several studies have suggested that in direct stenting there are shorter procedures with less radiation and contrast usage and less material consumption resulting in reduced procedural cost. Evidence to date indicates that direct stenting leads to similar late outcomes if compared to stenting after predilatation. Thus, on balance direct stenting has advantages over stenting after predilatation in appropriately selected patients: direct stenting compared to stenting after predilatation is feasible, safe, faster and more cost-effective with large clinical trials indicating similar late outcomes.

Chapter three describes a registry of direct stented patients with the use of a new stent in combination with a small guiding catheter (5F). A Blue Medical Devices Genic stent was used in all patients and a 5F catheter was inserted via the radial route. The combination of this new stent and 5F guiding catheter proved to be safe and effective in the performance of direct stent implantation and was associated with a high procedural success rate and favorable clinical outcomes up to a mean of 7 months after the procedure.

Chapter four shows that direct stenting is feasible and safe with high final success rate and low rate of complications. This technique is not compromized by the use of 6 French guides or the radial access, however, success rates are lower in more complex lesions, circumflex lesions, and longer lesions. With miniaturized equipment and improved stent systems with lower profiles and better stent fixation, direct stenting can be attempted in most patients suitable for elective stent implantation, resulting in a more efficient and probably safer treatment. The long-term outcome is favorable with a low target lesion revascularization rate. A randomized trial is needed for proper comparison, especially concerning the angiographic restenosis rates.

Chapter five This large randomized study proved that direct stenting was safe and effective in the treatment of single coronary artery lesions, with ultimate procedural success rates equivalent to stenting preceded by balloon dilatation. Direct stenting did not lead to the use of longer stents, and it was not associated with fewer dissections or distal embolizations. Lesion calcification was a predictor of failure of direct stenting. Although direct stenting was highly successful, its performance yielded only a modest cost saving compared with predilatation followed by stent placement.

Chapter six reports the long-term angiographic and clinical results of the study described in chapter five. In this patient population, with minimal exclusion criteria used direct coronary stenting and stent delivery preceded by balloon dilatation yielded an equally high overall procedural success rate. The 6-month rate of composite endpoint of MACCE, binary angiographic restenosis, target lesion revascularization rates and medical costs were not different between the two treatment intentions and similar to those reported in recently published stent trials. A second finding of this study is that an elevated baseline CRP level is a predictor of an adverse outcome after coronary stent implantation suggesting that an increased inflammatory activity is associated with a proliferative response within successfully implanted stents.

Chapter seven describes a clinical trial consisting of a registry and randomized phase investigating the in-hospital and long-term safety and effectiveness of direct stenting. In this selected patient population, stent delivery preceded by balloon dilatation and direct coronary stenting yielded similar overall procedural success rates. When direct stenting failed, the intervention typically proceeded with uneventful standard techniques, including predilatation. The 1-month rate of the composite endpoint of ischemic symptoms and/or major adverse cardiac events and cerebrovascular accidents, and the 9-month major adverse cardiac event rate were similar in both treatment groups. The procedural success and major adverse cardiac event rates observed in the non randomized phase of the study were similar to those measured in phase II. Finally, a modest cost saving was measured up to 9 months of follow up with the systematic use of the direct stenting strategy.

Chapter eight showed in an analysis on data from a prospective randomized trial comparing direct stenting with stenting after predilatation that cases performed by high-volume operators (case load: 4000) resulted in significantly faster procedures, less radiation time, lower contrast usage, lower need for postdilatation, lower procedural costs and most importantly a 50% reduction in six-month MACCE as compared to the low-volume physicians (case load: 75). For the low-volume group there was a significantly higher restenosis rate after direct stenting compared to stenting after predilatation. The technique direct stenting should therefore be reserved for high-volume operators. This study indicates that prolonged training periods and even more intensive supervision by experienced operators is mandatory.

Complete versus culprit vessel PCI in patients with multivessel disease
In current practice coronary interventions are usually restricted to the vessel responsible for ischemia (Culprit strategy). A complete or more complete strategy of all significant stenoses as present in patients with multivessel disease, might prevent future sequelae but could also lead to longer procedures, increased material consumption, more hospital admissions and a higher chance for restenosis. On the other hand, for the long-term more revascularizations could occur in the culprit group due to the initially untreated lesions. So far, the optimal approach for treatment of patients with multivessel disease eligible for PCI is not known.

Chapter nine In multivessel coronary disease, complete revascularization, i.e. PCI on all vessels with ≥50% stenosis, shows at short-term follow-up to be slightly more costly with no clinical advantages over culprit vessel PCI. Procedural success was higher in the culprit group. However, on the long-term more repeat PCIs were conducted in patients treated with culprit vessel PCI only, mostly because of the "untouched" stenoses as are left with culprit revascularization. Because of this, the incremental costs had become similar already after one year. The findings of this study indicate that the decision to perform culprit vessel PCI in patients with multivessel coronary artery disease remains a decision to be made on a case-by-case basis.

# Samenvatting

Dit proefschrift vergelijkt twee nieuwe therapeutische strategieën in de interventie cardiologie met de tot nu toe meest gangbare. Direct stenting (stenting zonder de vernauwing eerst voor te verwijden met een ballon) wordt vergeleken met de meer conventionele techniek van stenting na voorverwijden met een ballon. Het tweede onderdeel van dit proefschrift vergelijkt in patiënten met meertakslijden culprit vessel angioplastiek, dat wil zeggen behandeling van alleen het vat dat nu klachten veroorzaakt, met complete revascularisatie.

Direct stenting vergeleken met stenting na voorverwijden in een geselecteerde patiënten populatie met stabiele of instabiele angina pectoris:
Belangrijke ontwikkelingen in coronaire stent ontwerp hebben ervoor gezorgd dat een toenemend aantal interventie cardiologen een poging onderneemt om direct een stent te implanteren (direct stenting) zonder eerst de coronaire vernauwing voor te verwijden met een ballon (predilatatie).
Naast de waarschijnlijkheid dat direct stenting zou kunnen leiden tot verminderd materiaal gebruik, kortere procedures en kostenbesparing bestaat ook de hypothese dat direct stenting minder coronaire restenose veroorzaakt. Dit laatste zou dan komen door verminderde endotheel schade welke het re-endothelialisatie proces stimuleert. Aan de andere kant zou een directe en krachtige implantatie van de stent door de stenose aanzienlijk meer traumatisch kunnen zijn in vergelijking met ballon predilatatie. De uiteindelijke balans tussen deze tegenstrijdige effecten van direct stenting wordt gemaakt in dit proefschrift middels twee grote gerandomiseerde klinische trials, twee niet gerandomiseerde prospectieve studies en een overzicht van de literatuur. Het doel van deze studies was om de veiligheid, effectiviteit en kosten van direct stenting te onderzoeken in vergelijking met stenting voorafgegaan door predilatatie. Ook prediktoren voor succesvolle direct stent implantatie worden beschreven.

Hoofdstuk twee bestaat uit een literatuur studie die een overzicht geeft van recente studies die de haalbaarheid, veiligheid, klinische en economische resultaten van direct stenting onderzoeken. In goed geselecteerde laesies blijkt, dat direct stenting veilig en haalbaar is, en een effectieve methode om coronair ziekte te bestrijden. Het uiteindelijke procedurele succes van direct stenting is hoog met weinig complicaties, welke gelijk zijn aan die van stenting na predilatatie. Meerdere studies suggereren dat direct stenting leidt tot kortere procedures met minder doorlichtingstijd en contrast gebruik, minder materiaal consumptie, lagere procedurele kosten. Tot nu toe zijn er nog geen studies geweest die aantonen dat direct stenting leidt tot betere klinische of angiografische lange termijn resultaten.

Hoofdstuk drie omschrijft een registry van direct gestente patiënten gebruikmakend van een nieuwe stent in combinatie met smalle (5F) guiding catheters. Een Blue Medical Devices Genic stent en 5F guiding catheter, ingebracht via de radialis, werd bij alle

patiënten gebruikt. De combinatie van deze nieuwe stent met 5F guiding catheters bleek veilig en effectief voor het direct implanteren van een stent. Het was geassocieerd met een hoog procedureel succes en goede klinische resultaten tot 7 maanden na de procedure.

Hoofdstuk vier laat eveneens zien dat direct stenting haalbaar en veilig is met een hoog procedureel succes percentage. Direct stenting werd niet beïnvloed door het gebruik van 6F guiding catheters of gebruik van toegang tot de bloedbaan via de arteria radialis (polsarterie). Maar in complexere laesies, circumflex laesies of lange laesies waren de succes percentages lager. Deze studie liet zien dat de lange termijn resultaten na direct stenting goed zijn met een lage incidentie van target lesion angioplastiek.

Hoofdstuk vijf Dit is een grote gerandomiseerde studie die ook aantoont dat direct stenting veilig en effectief is in de behandeling van een enkele coronair laesie met procedurele succes percentages die gelijk zijn aan die van stenting na ballon dilatatie. Direct stenting resulteerde niet in het gebruik van langere stents, het was niet geassocieerd met minder dissecties of distale embolisaties. Laesie calcificatie was de enige onafhankelijke predictor voor het falen van direct stenting. Hoewel direct stenting erg succesvol bleek leverde het slechts een matig kostenvoordeel op in vergelijking met stenting na predilatatie.

Hoofdstuk zes rapporteert de klinische en angiografische resultaten op lange termijn (6 maanden) van dezelfde patiënten groep als vermeld in hoofdstuk 5. Grote cardiale en cerebrale problemen zoals dood, hartinfarct, rePCI, bypass operatie, hersenberoerte (MACCE), binaire angiografische restenosis, target lesion angioplastiek en kosten verschilden niet tussen direct stenting en stenting na predilatatie en waren gelijk aan de resultaten van recent gepubliceerde stent trials. Een tweede bevinding van deze studie is dat een gestegen baseline C-reactive proteïne spiegel een onafhankelijke voorspeller is voor een slecht kort en lange termijn klinisch resultaat en restenose. Het suggereert dat een toegenomen ontstekingsactiviteit geassocieerd is met een restenotisch proces in succesvol geïmplanteerde stents.

Hoofdstuk zeven is een klinische trial die bestaat uit een registry en gerandomiseerd onderdeel die de initiële en lange termijn veiligheid en effectiviteit onderzoeken van direct stenting. In deze geselecteerde patiënten populatie blijkt het procedureel succes van direct stenting niet te verschillen van stenting na predilatatie. De 1-maand MACCE en 9 maanden MACCE bleken ook gelijk in beide behandelingsgroepen. Het procedureel succes en MACCE waren gelijk tussen de registry en gerandomiseerde fase van dit onderzoek Een matig kostenvoordeel bestond voor direct stenting tot 9 maanden na de initiële procedure.

Hoofdstuk acht laat zien in een subgroep analyse van data van een grote gerandomiseerde trial, die direct stenting vergelijkt met stenting na predilatatie dat procedures die door ervaren operateurs (case load:4000) worden verricht in vergelijking

tot minder ervaren operateurs (case load:75) resulteren in significant snellere procedures, minder doorlichtingstijd, minder contrastgebruik, minder postdilatatie, lagere kosten en nog belangrijker een 50% reductie in 6 maanden MACCE. In de minder ervaren operateurs groep bleek een significant hoger restenosis percentage te bestaan na direct stenting in vergelijking met stenting na predilatatie. De techniek van direct stenting moet daarom behouden blijven voor meer ervaren operateurs. Deze studie impliceert dat langere trainingsperiodes voor minder ervaren operateurs en een nog intensievere begeleiding door ervaren operateurs noodzakelijk zijn.

Complete versus culprit vessel PCI in patiënten met meertakslijden
In de huidige praktijk worden coronaire interventies bij patiënten waarbij meerdere coronair arteriën tegelijk zijn aangedaan vaak beperkt tot het vat dat op dat moment verantwoordelijk is voor ischaemie (culprit strategie). Een complete revascularisatie van alle significante coronair stenoses zou kunnen leiden tot langere procedures, meer materiaal gebruik, meer ziekenhuisopnames en een hogere kans op restenose. Aan de andere kant zouden met alleen de culprit behandeling op langere termijn meer revascularisaties kunnen optreden door ischaemie ten gevolge van de onbehandelde laesie(s) na de culprit strategie. De optimale benadering om patiënten te behandelen met meertakslijden, die in aanmerking komen voor een coronaire interventie is niet bekend.

Hoofdstuk negen laat zien dat in patiënten met meertakslijden die in aanmerking komen voor angioplastiek en waarin een culprit laesie is aan te wijzen, complete revascularisatie d.w.z. van vaten met ≥50% stenose, met percutaneous coronary intervention (PCI) op korte termijn wat duurder is zonder duidelijke klinische voordelen in vergelijking met culprit vat PCI. Ook het procedurele succes was lager in de complete groep. Echter, op lange termijn werden er meer rePCIs gedaan in patiënten uit de culprit groep, meestal ten gevolge van een van de laesies die initieel onbehandeld waren gebleven. Hierdoor waren de kosten gemeten over 1 jaar al weer gelijkgetrokken tussen beide groepen. De resultaten uit deze studie wijzen erop dat het besluit om culprit of complete revascularisatie te verrichten gemaakt dient te worden op individuele basis.

# Abbreviations

| | |
|---|---|
| ACC/AHA type lesions | American College of Cardiology/American Heart Association lesion characteristics |
| Acute gain | MLD after stenting minus MLD at baseline |
| AP | Angina Pectoris |
| Atm | Atmosphere |
| CABG | Coronary Artery Bypass Grafting |
| CAD | Coronary Artery Disease |
| CCS | Classification of the Canadian Cardiovascular Society (cardiovascular disability assessment system). |
| CI | Confidence Interval |
| CK | Creatinine Kinase |
| CRP | C-reactive protein |
| CR | Complete revascularization |
| CVR | Culprit vessel revascularization |
| DIAG | Diagonal Coronary Artery |
| DSI | Direct Stent Implantation |
| DS | Diameter stenosis |
| € | Euro |
| ECG | Electrocardiogram |
| F | French |
| GP | Glycoprotein |
| LAD | Left Anterior Descending Coronary Artery |
| Late loss | MLD at follow-up minus MLD after stenting |
| LCx | Left Coronary Circumflex Artery |
| LM | Left Main |
| LV | Left ventricle |
| MACE | Major Adverse Cardiac Events |
| MACCE | Major Adverse Cardiac and Cerebral Events |
| MI | Myocardial Infarction |
| MLD | Minimal Lumen Diameter |
| MLDpost | Minimal lumen diameter after stenting |
| Net gain | MLD at follow-up minus MLD at baseline |
| NS | Not significant |
| PCI | Percutaneous Coronary Intervention |
| PREDIL | Stenting after predilatation |
| PTCA | Percutaneous Transluminal Coronary Angioplasty |
| QCA | Quantitative Coronary Angiography |
| RCA | Right Coronary Artery |
| SD | Standard Deviation |
| SVG | Saphenous Vein Graft |
| TIMI | Thrombolysis in Myocardial Infarction |
| TLR | Target Lesion Revascularization |

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## About the author

Sander IJsselmuiden was born February 1st 1975 in Nijmegen, the Netherlands. He attended the Jacob Roelands Lyceum in Boxtel, after which he started his medical study at the VU-medical center of Amsterdam in 1993. During his studies he was involved in a research project on rolling leukocytes in diabetic rats at the Institute for Cardiovascular research at the department of physiology at the VU-medical center (Head: Prof Geertjan Tangelder). Supported by a grant of the Netherlands Heart Foundation he did a clinical and research elective at the Cardiothoracic department of Duke University Medical Center (Durham, North Carolina, United States) for one year. He investigated the neurological damage, cognitive decline and bloodproduct usage after coronary bypass surgery and non-cardiac operations (Head: Prof. Mark F. Newman). He obtained his medical degree in 2000 at the VU university medical center, in Amsterdam. In the same year he started the studies described in this thesis at the Amsterdam Department of Intervention Cardiology, OLVG hospital (Head: Dr. Ferdinand Kiemeneij). Two times he received the young investigators award at the Intervention cardiology symposium in Amsterdam and the 9th annual scientific sessions of the BWGIC-WIC Invasive Cardiology. Currently he is working as a resident in Cardiology at the Onze Lieve Vrouwe Gasthuis in Amsterdam. He will start his Internal Medicine training in the Spaarne Haarlem hospital as part of the Cardiology residency program on February 2003.

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