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Direct stenting with the Bx VELOCITY™ balloon-expandable stent mounted on the Raptor® rapid exchange delivery system versus predilatation in a European randomized Trial: the VELVET trial

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AIMS: This study examined the six-month angiographic results of direct coronary stenting, and compared the nine-month safety, efficacy and cost of this strategy versus stenting after balloon predilatation.

METHODS: In phase I of VELVET, 122 patients (mean age = 62.3 ± 10.1 years, 77% male, 11% with diabetes) with angina pectoris or myocardial ischemia resulting from a single de novo 51% to 95% coronary stenosis underwent direct stenting. The endpoints of phase I included angiographic findings and rates of major adverse cardiac events up to six months of follow-up. In phase II, 401 patients (mean age = 61.3 ± 10.8 years, 79% male, 16% with diabetes) with angina pectoris or documented myocardial ischemia resulting from 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 nine months of follow-up were compared.

RESULTS: In phase I the mean diameter stenosis immediately before and after the procedure, and at six months was 61.7 ± 9.4%, 13.5 ± 6.3%, and 33.6 ± 16.2%, respectively. The six-month binary restenosis rate was 11%. The overall rate of major adverse cardiac events, including two 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 follow-up period of nine months, major adverse cardiac events rates were 12.0% and 10.9% in patients randomized to direct stenting and predilatation, respectively (non-significant). Analyses of the costs incurred up to nine months in each treatment group revealed a mean saving of €362 per patient in favor of the direct stenting strategy (non-significant).

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 nine 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 nine months. (Int J Cardiovasc Intervent 2003; 5: 17–26)

Keywords: coronary stent – direct stenting – predilatation - angioplasty – restenosis - coronary artery disease

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 the likelihood of saving cost and time, this strategy offers the hypothetical advantages of causing less injury and less endothelial denudation by immediate scaffolding of the vessel wall, thereby facilitating re-endothelializa-

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tion. 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 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.

Patient population and methods

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 ten European countries and the number of patients enrolled at each medical center is presented in the Appendix. The study was conducted in two 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 six-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 six-month performance of the Bx VELOCITY™ stent by quantitative coronary angiography. Its endpoints included: (1) incidence of major adverse cardiac events and cerebrovascular accidents up to 30 days, or symptomatic ischemia at the one-month visit (primary endpoint), and major adverse cardiac events up to six months after the index procedure; and (2) angiographic findings at the time of the procedure and after six months by quantitative coronary analysis. Major adverse cardiac events were defined as death from all causes, myocardial infarction, coronary artery bypass grafting, and further percutaneous target lesion interventions.

In phase II, 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 mm to 4.0 mm in diameter, which could be covered by one or two stents; these patients were followed clinically for nine 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 and cerebrovascular accidents up to 30 days or symptomatic ischemia at the one-month visit (primary endpoint), and major adverse cardiac events at nine months after the index procedure; (2) angiographic findings at the time of the procedure; and (3) medical costs and cost-effectiveness up to nine months after the index procedure. The definition of major adverse cardiac events in phase II was the same as indicated earlier, except for target vessel in place of target lesion interventions. 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 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. The clinical exclusion criteria for both phases were: 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. 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 the investigator obtained informed consent and verification of all eligibility criteria.

Stents and delivery system, and procedural characteristics

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

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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 four weeks.

Patient follow-up

Patients returned at 30 days and six months (those enrolled in phases I and II), and at nine months (those enrolled in phase II), 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 six-month follow-up angiography for quantitative coronary analysis. The six-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 six 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 six months in phase I patients. Minimal luminal diameter and % diameter stenosis (%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 two treatment strategies included costs of the initial procedure, and resources used until discharge from the hospital and up to nine 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 nine 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 nine months' 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 four quadrants of the cost-effectiveness plane was assessed by calculating (by a Gaussian method) the appro-

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priate 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

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. However, all Bx VELOCITY™ stents were successfully withdrawn after the direct stenting attempt.

The mean duration of hospitalization for the index procedure was 2.5 ± 1.2 days. The angiographic follow-up at six 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 six months. The restenosis rate among 99 patients who underwent follow-up angiography at six months was 11%.

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 patients who could be analyzed (Table 2). Table 2 also lists the numbers of major adverse cardiac events (including two non-cardiac deaths) recorded between the index procedure and 180 days. One patient died of rapidly evolving lung carcinoma at 110 days, and the other of profound ticlopidine-induced thrombocytopenia at 23 days. The overall proportion of patients free from major adverse cardiac events and free from target lesion revascularization at six months in phase I 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 having more than one 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 two 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

Age, y (mean ± SD)	62.3 ± 10.1
Male/female	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.

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

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Measurement (n = number of observations available for analysis)		*p*-value
Reference vessel diameter, mm (n):		
before procedure	2.80 ± 0.56 (122)	–
after procedure	2.95 ± 0.46 (121)	0.0001
six 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
six 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
six 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 MACE:		
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 MACE	12 (9.8)	

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

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

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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 two groups was 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 two 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 two 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, compared with 25.8% of procedures preceded by balloon dilatation ($p < 0.001$).

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.

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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
Male/female	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 or lesions.

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

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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 (non-significant). Likewise, no difference was found between the two groups in overall rates of major adverse cardiac events and cerebrovascular events at one month (3.0% in both groups, Table 4). Two patients randomized to predilatation died out of hospital, one due to presumed stent thrombosis three days after the index procedure, and the other due to cerebrovascular accident 25 days after the index procedure. One patient randomized to direct stenting died of presumed stent thrombosis 28 days after the index procedure.

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 having more than one stent implanted (odds ratio 3.442, $p = 0.01$), were independent predictors of recurrent ischemic events at the one-month visit, or major adverse cardiac events and cerebrovascular accidents at 30 days.

Long-term adverse clinical events

At 270 days after the index procedure, major adverse cardiac events had occurred in 24 of 200 (12.0%) patients randomized to direct stenting, versus 22 of 201 (10.9%) patients randomized to predilatation (non-significant, Table 4). One patient randomized to direct stenting died of acute thrombotic occlusion in a non-target vessel after an intracoronary ultrasound examination, 269 days 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 event-free survival is shown in Figure 2B. Neither analysis showed a difference between the two groups.

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

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Quantitative angiographic analysis	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* (mean ± SD)	13.9 ± 6.8	12.5 ± 6.3
In-segment % diameter stenosis (mean ± SD)	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. * $p < 0.05$. ** Primary endpoint phase II = symptomatic ischemia at the one-month visit or major adverse cardiac events and cerebrovascular accidents at 30 days. MLD = minimal luminal diameter; MACE = major adverse cardiac events.

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

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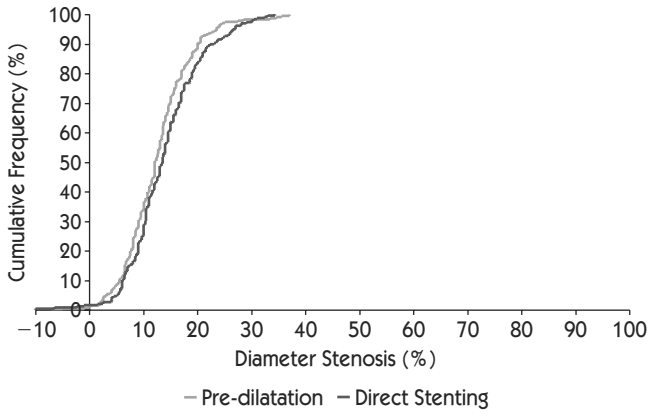

Figure 1
Cumulative distribution of postprocedural %DS in both treatment groups of phase II.

€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 reduced use of angioplasty balloons (€463). At the time of discharge from the hospital, the average cost per patient was €3857 in the direct stenting group, versus €4401 in the predilated group ($p = 0.0001$ Wilcoxon; $p < 0.001$ *t*-test). Between discharge of the patient from hospital and the end of follow-up, the mean cost per patient was €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 four patients undergoing coronary artery bypass graft surgery, in contrast to a single patient in the predilated group. At nine months, the overall cost per patient was €6698 in patients randomized to direct stenting versus €7060 in patients randomized to predilatation ($p = 0.0171$ Wilcoxon; $p = 0.5149$ *t*-test). The absence of a

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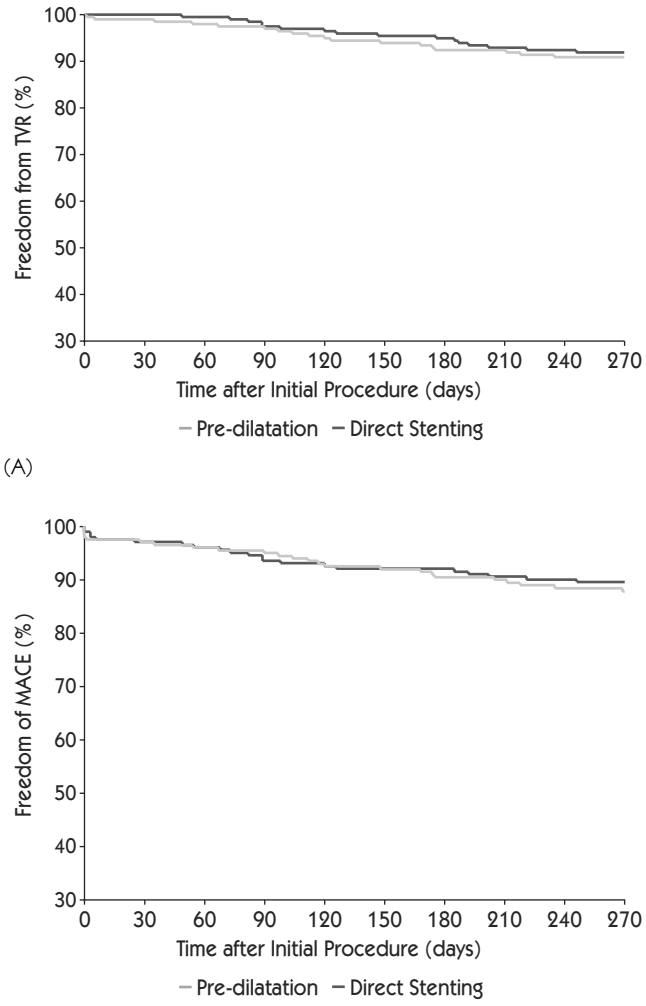

Figure 2
(A) Kaplan-Meier survival free from target vessel revascularization in Phase II of VELVET (B) Kaplan-Meier survival free from major adverse cardiac events in Phase II of VELVET.

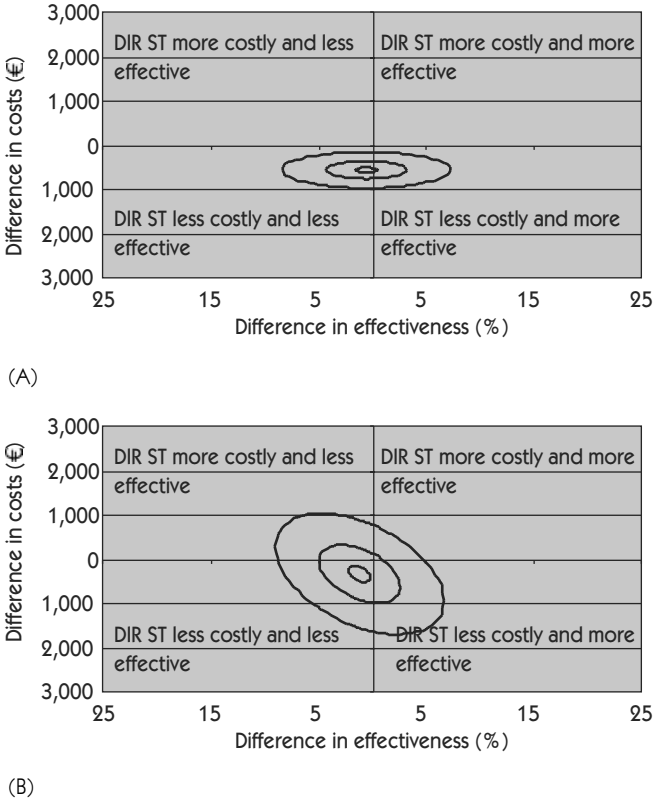

Figure 3
(A) Procedure-related cost-effectiveness analysis of direct stenting (DIR ST) versus predilatation. Inner ellipse = 5% probability; middle ellipse = 50% probability; outer ellipse = 50% probability. (B) Cost-effectiveness analysis of direct stenting versus predilatation up to 270 days.

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).

Discussion

The sequential design of this study, which included a non-randomized phase followed by a randomized phase, allowed us to: (1) examine separately the six-month angiographic outcomes of the direct stenting strategy, and (2) compare separately its effects on clinical events and medical costs up to nine 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 1

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 six-month restenosis (11%) and target lesion 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 six-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

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Cost item	Direct stenting	Predilatation
Procedure time	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 NINE-MONTH COSTS	**6698**	**7060*****

Values represent mean cost per patient (± SD) in Euros. Mean procedure times were 59.3 min in the direct stenting group versus 63.8 min in the predilated group.
*$p < 0.0001$; **$p < 0.001$; ***non-significant.

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

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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 owing 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 two 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 strategy of systematic direct stenting with provisional predilatation 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, which was designed uniquely 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 nine months, the difference was no longer significant due to the considerable costs resulting from additional hospitalizations and procedures during long-term follow-up, and increased 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 one-month rate of the composite endpoint of ischemic symptoms and/or major adverse cardiac events and cerebrovascular accidents, and the nine-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 nine 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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C Macaya, *Hospital Clinico San Carlos, Madrid, Spain* (35)
P Boekstegers, *Klinikum Grosshadern, München, Germany* (32)
A Colombo, *Centro Cuore Colombus, Milano, Italy* (29)
O Wittenberg, *Clinique Les Franciscaines, Nimes, France* (28)
K Khalife, *CHR Bon Secours, Metz, France* (26)
H Kelbaek, *Heart Center, Rigshospitalet, Copenhagen, Denmark* (24)
G Richardt, *Med. Universität Lübeck, Lübeck, Germany* (24)
F Fernandez-Aviles, *Hospital Universitario de Valladolid, Valladolid, Spain* (22)
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J Schofer, *Kardiologische Gemeinschaftspraxis, Hamburg, Germany* (16)
J Fajadet, *Clinique Pasteur, Toulouse, France* (5)
N Buller, *The Queen Elizabeth Hospital, Birmingham, United Kingdom* (4)
P Barragan, *Polyclinique Les Fleurs, Ollioules, France* (2).

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