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Drug-Eluting Stents in the Treatment of Intermediate Lesions

Pooled Analysis From Four Randomized Trials

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OBJECTIVES To address the safety and efficacy of drug-eluting stents (DES) in the treatment of intermediate lesions, we performed a pooled analysis of four randomized DES versus bare-metal stent (BMS) trials and assessed outcomes among patients with intermediate lesions.

BACKGROUND Before the introduction of DES, intermediate coronary lesions were commonly managed based on physiologic or anatomic assessment of lesion severity. The DES may challenge this paradigm.

METHODS The study population involved 167 of 2,478 randomized patients (6.7%) with intermediate lesions (diameter stenosis <50% [mean 44%] by quantitative coronary angiography) from the Sirolimus-coated Bx Velocity Balloon Expandable Stent in the Treatment of Patients with De Novo Coronary Artery Lesions (SIRIUS), TAXUS-IV, and the First and Second First Use to Underscore Restenosis Reduction with Everolimus (FUTURE-I and -II) trials. End points examined included early (in-hospital and 30-day) and late (1-year) major adverse cardiac events (MACE), including cardiac death, myocardial infarction (MI), target vessel revascularization (TVR), stent thrombosis, and follow-up angiographic restenosis.

RESULTS Patients with intermediate lesions randomized to DES versus BMS had low rates of 30-day MACE (1.1% vs. 4.0% respectively; $p = 0.22$). At one-year follow-up, patients treated with DES versus BMS had similar rates of cardiac death (0% vs. 2.7%, respectively; $p = 0.11$) and MI (3.4% vs. 5.4%; $p = 0.49$) but markedly lower rates of TVR (3.4% vs. 20.3%; $p = 0.0004$), MACE (5.6% vs. 25.4%; $p = 0.0003$), and binary angiographic restenosis (1.8% vs. 34.0%; $p < 0.0001$). No patient in either group developed stent thrombosis.

CONCLUSIONS Compared with BMS, treatment of intermediate lesions with DES appears safe and results in a marked reduction in clinical and angiographic restenosis. The efficacy of DES may require a reevaluation of current treatment paradigms for intermediate lesions. (J Am Coll Cardiol 2006;47:2164–71) © 2006 by the American College of Cardiology Foundation

Intermediate coronary lesions are frequently found on diagnostic coronary angiography. The decision whether to treat such lesions continues to be a challenge. In the presence of typical angina and evidence of ischemia on the noninvasive testing, revascularization is usually warranted (1). If the results of noninvasive testing are not available, inconclusive, or contradictory, or if more than one intermediate lesion is present in the same vessel, adjunctive diagnostic modalities to guide management are recommended (2–6). Such modalities include assessment of the physiologic significance of the lesion using pressure-derived myocardial fractional flow reserve (FFR) or the evaluation of the luminal dimensions and morphology of the atherosclerotic plaque and vascular wall using intravascular ultrasound (IVUS) (2–6). In several studies, deferring of coronary intervention for intermediate stenosis with normal physiology (FFR ≥0.75) was consistently associated with relatively low (6.3% to 11%) rates of major adverse cardiac events (MACE) during follow-up ranging from six months to three years (7–10). Likewise, medically treated patients with minimal luminal area ≥4.0 mm^2 by IVUS had only an 8% rate of cardiac events at mean follow-up of 13 months (11). In general, deferred intervention based on these criteria has been associated with fewer clinical events than a deliberate interventional strategy (7,9,10).

Introduction of drug-eluting stents (DES) into clinical practice may potentially challenge this paradigm for the management of intermediate lesions. However, scant data have been reported on the safety and efficacy of DES in the treatment of patients with intermediate coronary lesions. In a small series of 20 consecutive patients with 23 angiographically mild (<50% by quantitative coronary angiog-

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Abbreviations and Acronyms

BMS = bare-metal stent
DES = drug-eluting stent
FFR = fractional flow reserve
IVUS = intravascular ultrasound
MACE = major adverse cardiac events
MI = myocardial infarction
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography
TLR = target lesion revascularization
TVR = target vessel revascularization

raphy [QCA]), de novo lesions from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital [RESEARCH] registry treated with sirolimus-eluting stents, survival free of MACE was 95% at a mean follow-up of 399 days with no cases of target lesion revascularization (12). To further address the question of safety and efficacy of DES in the treatment of intermediate lesions, we performed a patient-level pooled analysis of four randomized DES versus bare-metal stent (BMS) trials and assessed the outcomes among patients undergoing percutaneous coronary intervention (PCI) for intermediate lesions.

METHODS

Patient population. This study represents a retrospective analysis of patients with intermediate target lesions (<50% diameter stenosis as defined by QCA) from four randomized DES versus BMS clinical trials. The choice of trials was based on the similarity of clinical and angiographic characteristics for the entry into the trial. The individual data of patients from the following four prospective, randomized, and controlled trials were pooled: Sirolimus-Coated Bx Velocity Balloon Expandable Stent in the Treatment of Patients With de Novo Coronary Artery Lesions (SIRIUS), TAXUS-IV, and the first and second First Use to Underscore Restenosis Reduction With Everolimus (FUTURE-I and -II). Outcomes were assessed in-hospital, at 30 days, and at 1 year.

The protocols and the principal results of SIRIUS, TAXUS-IV, FUTURE-I, and FUTURE-II trials have been reported elsewhere (13–19). Briefly, in the SIRIUS trial, 1,058 patients at 53 U.S. centers were randomized to a sirolimus-eluting or a bare-metal Bx Velocity stent (both from Cordis Corp., Warren, New Jersey) (13,14). The TAXUS-IV study was a randomized trial that compared outcomes of 1,314 patients at 73 U.S. centers treated with the slow-release, polymer-based, paclitaxel-eluting Taxus stent or a bare-metal Express stent (both from Boston Scientific Corp., Natick, Massachusetts) (15,16). In the FUTURE-I trial, 42 nondiabetic patients at a single center were randomized in a 2:1 mode to either an everolimus-eluting Challenge EES stent or the bare-metal S-Stent (both from Biosensors International, Singapore) (17,18). Subsequently, 64 patients at four centers were randomized 1:1 to the Challenge EES stent or the bare-metal S-Stent in the FUTURE-II trial (19).

Common to all four trials, patients with stable or unstable angina or inducible ischemia underwent stent-assisted PCI for a single de novo lesion (stenosis of 51% to 99% of the luminal diameter by visual assessment on baseline angiography) in a native coronary artery coverable by a single study stent. Target lesion length was 15 to 30 mm in the SIRIUS trial, 10 to 28 mm in the TAXUS-IV trial, and ≤18 mm in the FUTURE-I and -II trials. Diameters of study and control stents were 2.5, 3.0, and 3.5 mm in all of the trials, and stents 4.0 mm in diameter also were available in the FUTURE-I and -II studies. The recommended duration of clopidogrel treatment post-PCI was six months in all the trials with the exception of the SIRIUS trial that advocated therapy with clopidogrel for three months. Primary end points differed across the trials: nine-month target vessel failure (cardiac death, myocardial infarction [MI], or target vessel revascularization [TVR]) in the SIRIUS trial; nine-month TVR in the TAXUS-IV trial; 30-day MACE, including death, target lesion revascularization (TLR), or MI in the FUTURE-I trial; and in-stent late loss in the FUTURE-II trial. By study protocol, angiographic follow-up was performed at eight months in SIRIUS, nine months in the TAXUS-IV trial, and six months in the FUTURE-I and -II trials.

Definitions and clinical end points. In all trials the definition of MI was creatinine kinase greater than twice the upper limit of the normal range accompanied by an elevated level of creatine kinase-MB in the absence or presence of new pathologic Q waves on the electrocardiogram (for non–Q- or Q-wave MI, respectively). The definition of TLR was also identical across trials: any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for recurrent angina, ischemia, or QCA diameter stenosis ≥70%. Target vessel revascularization was defined as any clinically driven repeat PCI of the target vessel or bypass surgery of the target vessel. In each trial, all clinical end points were adjudicated by an independent clinical events committee blinded to the treatment assignment.

Quantitative coronary angiography. Quantitative angiographic measurements were performed by an independent angiographic core laboratory which was blinded to the treatment assignment: the Brigham and Women's Angiographic Core Laboratory, Boston, Massachusetts, for the SIRIUS and TAXUS-IV trials and the Angiographic Core Laboratory of the Cardiovascular Research Foundation, New York, New York, for the FUTURE-I and -II trials. Measurements included the stented segment (in-stent) as well as the lesion segment (the stented segment plus margins 5 mm proximal and distal to the stent [analysis segment]). For the purposes of the present report, an intermediate lesion was defined by baseline QCA as <50% diameter stenosis. Binary restenosis at angiographic follow-up was defined as diameter stenosis >50%.

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Statistical analysis. Continuous variables are expressed as mean ± 1 standard deviation and compared by unpaired Student *t* test. Categoric data are presented as frequencies and percentages and are compared using the Fisher exact test. Out-of-hospital outcomes were estimated by the Kaplan-Meier method and compared using log rank tests. Adjusted event rates were determined using a multivariate Cox proportional hazards model to control for significant ($p < 0.05$) baseline covariates. All tests were two sided with a significance level of 0.05. Heterogeneity of the treatment effect on major outcomes across the trials was tested using a Cox proportional hazards model with a study × treatment interaction term included, also controlling for baseline patient characteristics. The significance of interaction was evaluated using the likelihood ratio test.

RESULTS

Baseline clinical and angiographic characteristics. Of the 2,478 lesions randomized to DES versus BMS in the four trials, 167 lesions (6.7%) were of intermediate severity, including 101 of 1,058 (9.5%) in the SIRIUS trial, 52 of 1,314 (3.9%) in the TAXUS-IV trial, and 14 of 106 (13.2%) in the FUTURE-I and -II trials. A total of 92 lesions were treated with a DES (57 in the SIRIUS trial, 29 in the TAXUS-IV trial, and 6 in the FUTURE-I and -II trials), and 75 lesions with a BMS (44, 23, and 8, respectively).

Baseline clinical and angiographic data of patients from the pooled analysis assigned to DES versus BMS are presented in Table 1. Patients treated with DES compared to those treated with BMS tended to be older, had a higher frequency of unstable angina at clinical presentation, and were more frequently treated with PCI in the past. Other characteristics were closely matched between the groups. Baseline and post-procedure angiographic measures and procedure characteristics also did not differ significantly between the patients treated with DES and BMS (Tables 1 and 2). Pre-procedure target lesion diameter stenosis ranged from 24.6% to 49.9% in the DES group and from 25.5% to 49.9% in the BMS group.

Table 1. Baseline Clinical Characteristics and Angiographic Features

	DES (n = 92)	BMS (n = 75)	p
Clinical characteristics			
Age (yrs)	64.2 ± 11.9	60.8 ± 11.7	0.06
Male gender (%)	70.7	65.3	0.51
Diabetes mellitus (%)	21.7	27.0	0.47
Hypertension (%)	70.7	73.0	0.86
Hyperlipidemia (%)	74.2	69.3	0.60
Current smoking (%)	18.0	24.7	0.33
Prior myocardial infarction (%)	25.3	22.7	0.72
Prior PCI (%)	38.0	21.3	0.03
Prior coronary bypass surgery (%)	12.0	4.0	0.09
Unstable angina (%)	42.4	28.0	0.07
Angiographic features			
Lesion length (mm)	11.4 ± 4.83	11.2 ± 4.44	0.76
Reference vessel diameter (mm)	2.85 ± 0.46	2.86 ± 0.51	0.86
Minimal luminal diameter (mm)	1.59 ± 0.31	1.63 ± 0.35	0.42
Diameter stenosis (%)	44.3 ± 5.3	43.1 ± 6.4	0.21
Target artery (%)			
Left anterior descending artery	50.0%	58.7%	0.28
Left circumflex artery	19.6%	18.7%	1.00
Right coronary artery	29.3%	22.7%	0.37
TIMI flow grade 3 (%)	98.9%	100.0%	1.0
Left ventricle ejection fraction (%)	56.8 ± 9.8	58.6 ± 10.9	0.24

BMS = bare-metal stent; DES = drug-eluting stent; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

Table 2. Procedure Results

	DES (n = 92)	BMS (n = 75)	p
Final reference-vessel diameter (mm)	2.89 ± 0.43	2.89 ± 0.49	0.91
Final minimal luminal diameter (mm)			
Analysis segment	2.43 ± 0.46	2.45 ± 0.47	0.81
In-stent	2.78 ± 0.44	2.76 ± 0.41	0.74
Final diameter stenosis (%)			
Analysis segment	15.87 ± 7.75	18.85 ± 10.4	0.92
In-stent	3.51 ± 8.99	2.82 ± 11.05	0.73
Acute gain (mm)			
Analysis segment	0.85 ± 0.27	0.83 ± 0.30	0.71
In-stent	1.19 ± 0.31	1.14 ± 0.27	0.22
TIMI flow grade 3 (%)	100.0%	100.0%	—
Use of IIb/IIIa receptor inhibitors (%)	50.0%	41.3%	0.28
Procedure success (%)	98.8%	97.0%	0.58

Abbreviations as in Table 1.

In-hospital and 30-day outcomes. In-hospital MACE occurred rarely and with similar frequency in both groups (Table 3). The only in-hospital event in patients treated with DES was one case of a non–Q-wave MI (in the SIRIUS trial). In patients treated with BMS, there were two cases of non–Q-wave MI (2.7%) (one patient in the SIRIUS trial and one in the TAXUS trial).

At 30-day follow-up, no additional MACE occurred in patients treated with DES whereas there was one more non–Q-wave MI in patients treated with BMS (in the SIRIUS trial). As a result, 30-day MACE rates were 1.1% versus 4.0%, respectively ($p = 0.22$). There were no early stent thromboses in either group.

When stratified by the stent type and peri-procedure administration of platelet glycoprotein IIb/IIIa inhibitors (Table 4), outcomes were not related to the treatment with glycoprotein IIb/IIIa inhibitors in patients that underwent implantation of DES (at 30 days, 0% vs. 2.2% patients that were treated with glycoprotein IIb/IIIa inhibitors vs. those who had not experienced MI or MACE; $p = 0.32$), whereas in patients that underwent implantation of BMS there was a trend toward decreased incidence of 30-day MI and MACE in patients treated versus not treated with glycoprotein IIb/IIIa inhibitors (0% vs. 6.8%, respectively; $p = 0.14$). Notably, at 30 days, patients treated with glycoprotein IIb/IIIa inhibitors in both DES and BMS groups were completely free from cardiac events.

Table 3. Clinical Outcomes

	DES (n = 92)	BMS (n = 75)	p
In-hospital			
Cardiac death, n (%)	0 (0)	0 (0)	—
Myocardial infarction, n (%)	1 (1.1%)	2 (2.7%)	0.58
Target vessel revascularization, n (%)	0 (0)	0 (0)	—
Composite adverse cardiac events, n (%)*	1 (1.1%)	2 (2.7%)	0.58
30-day (cumulative)			
Cardiac death, n (%)	0 (0)	0 (0)	—
Myocardial infarction, n (%)	1 (1.1%)	3 (4.0%)	0.22
Target vessel revascularization, n (%)	0 (0)	0 (0)	—
Composite adverse cardiac events, n (%)*	1 (1.1%)	3 (4.0%)	0.22
1-yr (cumulative)			
Cardiac death, n (%)	0 (0)	2 (2.7)	0.11
Myocardial infarction, n (%)	3 (3.4)	4 (5.4)	0.49
Q-wave	0 (0)	0 (0)	—
Non–Q-wave	3 (3.4)	4 (5.4)	0.49
Stent thrombosis, n (%)	0 (0)	0 (0)	—
Target lesion revascularization, n (%)	1 (1.2)	15 (20.3)	<0.0001
Target vessel revascularization, n (%)	3 (3.4)	15 (20.3)	0.0004
Composite adverse cardiac events, n (%)*	5 (5.6)	19 (25.4)	0.0003

*Defined as the composite occurrence of either cardiac death or myocardial infarction or target vessel revascularization for ischemia.
Abbreviations as in Table 1.

One-year outcomes. One-year clinical follow-up was available in all patients (Table 3). In patients treated with DES, there were no cardiac deaths, two additional non–Q-wave MIs (in the SIRIUS trial), one TLR (in the SIRIUS trial), and three TVRs (two in the SIRIUS trial and one in the TAXUS-IV trial). Among patients treated with BMS, there were two cardiac deaths (in the SIRIUS trial), one additional non–Q-wave MI (in the SIRIUS trial), and 15 recurrences requiring either TLR or TVR (11 in the SIRIUS trial, 3 in the TAXUS-IV, and 1 in the FUTURE-I and -II trials). As a result, treatment with BMS rather than DES was associated with significantly higher rates of one-year TLR (20.3% [95% confidence interval (CI) 9.4% to 31.1%] vs. 1.2% [95% CI 0% to 4.0%]), TVR (20.3% [95% CI 9.4% to 31.1%] vs. 3.4% [95% CI 0% to 7.7%]), and MACE (25.4% [95% CI 13.6% to 37.3%] vs. 5.6% [95% CI 0.1% to 11.1%]) and with lower event-free survival (Fig. 1). After controlling for significant baseline covariates, patients treated with DES compared with patients treated with BMS still had significantly lower one-year TLR (1.2% vs. 20.3%; $p < 0.0001$), TVR (3.2 vs. 19.2%; $p = 0.004$), and composite MACE (4.1% vs. 23.5%; $p = 0.001$). Of note, no patient in either group developed stent thrombosis through one-year follow-up.

Testing for the heterogeneity of the treatment effect using multivariate models with and without study × treatment

Table 4. Clinical Outcomes Stratified by Stent Type and Peri-Procedure Administration of Platelet Glycoprotein IIb/IIIa Inhibitors

	DES			BMS		
Outcomes	(+) IIb/IIIa n = 46	(−) IIb/IIIa n = 46	p	(+) IIb/IIIa n = 31	(−) IIb/IIIa n = 44	p
In-hospital						
Cardiac death, n (%)	0 (0)	0 (0)	—	0 (0)	0 (0)	—
MI, n (%)	0 (0)	1 (2.2%)	1.0	0 (0)	2 (4.5%)	0.51
TVR, n (%)	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Composite adverse cardiac events, n (%)*	0 (0)	1 (2.2%)	1.0	0 (0)	2 (4.5%)	0.51
30-day (cumulative)						
Cardiac death, n (%)	0 (0)	0 (0)	—	0 (0)	0 (0)	—
MI, n (%)	0 (0)	1 (2.2%)	0.32	0 (0)	3 (6.8%)	0.14
TVR, n (%)	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Composite adverse cardiac events, n (%)*	0 (0)	1 (2.2%)	0.32	0 (0)	3 (6.8%)	0.14
1-yr (cumulative)						
Cardiac death, n (%)	0 (0)	0 (0)	—	0 (0)	2 (4.7%)	0.23
MI, n (%)	1 (2.2%)	2 (4.3%)	0.52	0 (0)	4 (9.2%)	0.08
TLR, n (%)	1 (2.2%)	0 (0)	0.34	6 (19.4%)	9 (21.0%)	0.82
TVR, n (%)	1 (2.2%)	2 (4.3%)	0.52	6 (19.4%)	9 (21.0%)	0.82
Composite adverse cardiac events, n (%)*	1 (2.2%)	4 (8.7%)	0.15	6 (19.4%)	13 (29.7%)	0.28

*Defined as the composite occurrence of either cardiac death or myocardial infarction or target vessel revascularization for ischemia.
MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

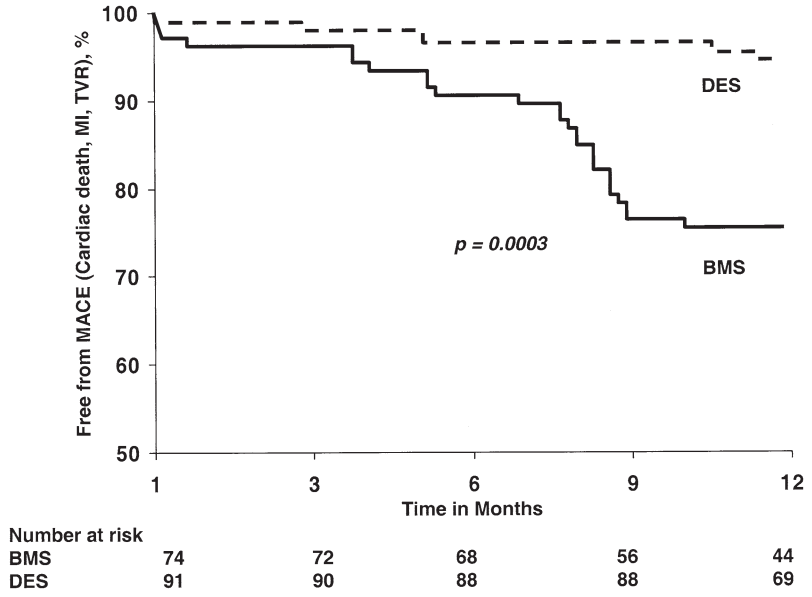

Figure 1. One-year survival free from major adverse cardiac events (MACE) of patients with intermediate lesions randomized to drug-eluting stents (DES) versus bare-metal stents (BMS). MI = myocardial infarction; TVR = target vessel revascularization.

interaction term and adjustment for significant baseline characteristics showed that the interaction term was not significant from the likelihood ratio test (p = 0.29 and p = 0.99 for one-month and one-year MACE, respectively). Therefore, the treatment effect was homogeneous across studies.

Angiographic follow-up. Angiographic follow-up was available in 57 of 92 patients (61.9%) treated with DES and 53 of 75 patients (70.6%) treated with BMS (p = 0.19) (Table 5). In-stent segment binary restenosis rates were markedly reduced in patients treated with DES compared with patients receiving a BMS (1.8% vs. 32.1%; difference −30.3% [95% CI −49.3% to −12.8%]). The same was true with regard to rates of in-lesion binary restenosis (1.8% vs. 34.0%; difference −32.2% [95% CI −51.0% to −14.7%]). Patients randomized to a DES had a significantly larger minimal luminal diameter, lower diameter stenosis, and less late loss at follow-up than patients assigned to receive a BMS.

Table 5. Angiographic Follow-Up Findings

	DES (n = 57)	BMS (n = 53)	p
Reference-vessel diameter (mm)	2.91 ± 0.47	2.87 ± 0.45	0.65
Minimal luminal diameter (mm)			
Analysis segment	2.38 ± 0.54	1.81 ± 0.75	<0.0001
In-stent	2.68 ± 0.57	1.96 ± 0.86	<0.0001
Diameter stenosis (%)			
Analysis segment	18.4 ± 11.1	37.9 ± 21.5	<0.0001
In-stent	7.4 ± 14.2	33.2 ± 24.8	<0.0001
Late loss (mm)			
Analysis segment	0.15 ± 0.34	0.68 ± 0.71	<0.0001
In-stent	0.15 ± 0.38	0.86 ± 0.71	<0.0001
Binary restenosis rate (%)			
Analysis segment	1.8%	34.0%	<0.0001
In-stent	1.8%	32.1%	<0.0001

Abbreviations as in Table 1.

DISCUSSION

The principal findings of this pooled analysis of the outcomes of patients with intermediate coronary lesions randomized to DES versus BMS are as follows. 1) Due to overestimation of the stenosis severity by visual assessment, 6.7% (95% CI 3.9% to 13.2%) of patients in the analyzed randomized trials had lesions with diameter stenosis <50% by QCA, generally considered as mild or intermediate in severity. 2) The treatment of intermediate lesions with DES was safe, with very low rates of in-hospital and 30-day complications, and no stent thromboses at one year. 3) When compared with BMS, DES resulted in a marked reduction in restenosis and, consequently, dramatically lower rates of TLR, TVR, and MACE at one-year follow-up.

Frequency and definition of an intermediate lesion. Each of the four trials' inclusion criteria required a lesion diameter stenosis >50% by visual assessment. However, 6.7% of the patients in this pooled analysis had lesion diameter stenosis <50% when assessed objectively using QCA (mean stenosis severity 44%). This incidence is comparable to the data on the incidence of intermediate lesions (using the same definition) reported from a pooled analysis from 14 randomized studies and registries of patients treated with balloon angioplasty (8.3%) or BMS (4.1%) (20).

Of note, there is no consensus regarding the definition of intermediate lesion in the literature. The "visual estimation" definition of an intermediate lesion was 30% to 70% in studies by Miller et al. (21) and Meuwissen et al. (22), 40%

to 70% in studies by Bech et al. (23) and Chamuleau et al. (8), 50% in a study by Pijls et al. (4), and <70% in a study by Abizaid et al. (11). Even so, the 44% mean diameter stenosis at the site of intermediate lesions as measured by QCA was similar in this analysis to the other studies on intermediate lesions reporting QCA data (4,11,22,23).

Given the cost of DES, more precise assessment of intermediate lesions such as online QCA, IVUS, or invasive physiology is warranted.

Treatment of intermediate lesions with BMS. In this current pooled analysis, treatment of intermediate lesions with BMS was associated with a 25.4% rate of MACE at one-year follow-up, similar to that reported from the pooled analysis of 14 randomized studies and registries using stents of earlier design (22%) (20). In both pooled analyses the majority of MACE was attributed to TLR and TVR (20.3% and 18.7%, respectively). Furthermore, the 25.4% one-year MACE rate with BMS in the current report was substantially higher than both the 11.1% and 17.8% two-year rates observed with the deferred PCI strategies in intermediate lesions with FFR ≥0.75 and similar to the 29.2% two-year MACE rate with PCI in intermediate lesions with FFR <0.75 in the Deferral Versus Performance of Percutaneous Transluminal Coronary Angioplasty in Patients Without Documented Ischemia trial (7). These findings extend even to lesions with diameter stenosis <50%. Collectively, these data suggest that BMS should not routinely be used to treat intermediate lesions without further physiologic or anatomic delineation.

Treatment of intermediate lesions with DES. In contrast, patients in the present analysis in whom intermediate lesions were treated with DES had very low rates of early and late clinical events. No patient died or developed Q-wave MI or stent thrombosis. Rates of non–Q-wave MI were low (3.4% [95% CI 0% to 7.1%]) and not unquestionably were attributed to the target lesion or vessel. A remarkably low rate of angiographic restenosis (1.8% [95% CI 0.1% to 8.9%]) was observed in intermediate lesions treated with DES at follow-up angiography. As a result, only one patient (1.2%) required TLR at one-year after DES implantation in an intermediate lesion. Although neither IVUS nor physiologic testing of the intermediate lesions in these trials was performed to determine which were ischemia producing or anatomically significant, the one-year observed MACE rate of 5.6% compares favorably with historical control MACE rates from studies in which PCI was deferred based on these tests (Fig. 2) (7–11,23). The safety of treating intermediate lesions with DES extends even to lesions with diameter stenosis <50%.

Remarkable also is the absence of 30-day events in patients treated with platelet glycoprotein IIb/IIIa inhibitors. Assuming this therapy has been given to the high-risk patients with unstable angina or unfavorable angiographic characteristics (e.g., ulcerated plaque or thrombus-containing lesion), the low event rate in this cohort is of particular importance.

Potential clinical implications. The highly favorable outcomes in patients with intermediate coronary lesions treated with DES in the present study should not be interpreted as a current call to liberalize the well-accepted criteria for intervention in lesions likely to be of hemodynamic significance. However, given the low risk of adverse events and restenosis with DES in this study, the results of the present study may impact trial design investigating future strategies to prevent plaque rupture and progression of atherosclerosis.

Though prospective randomized trials will be required to validate the safety, efficacy, and cost effectiveness of prophylactic DES implantation, baseline elevation of inflammatory markers may help identify which intermediate lesions may be at imminent risk for progression. Meuwissen et al. (22)

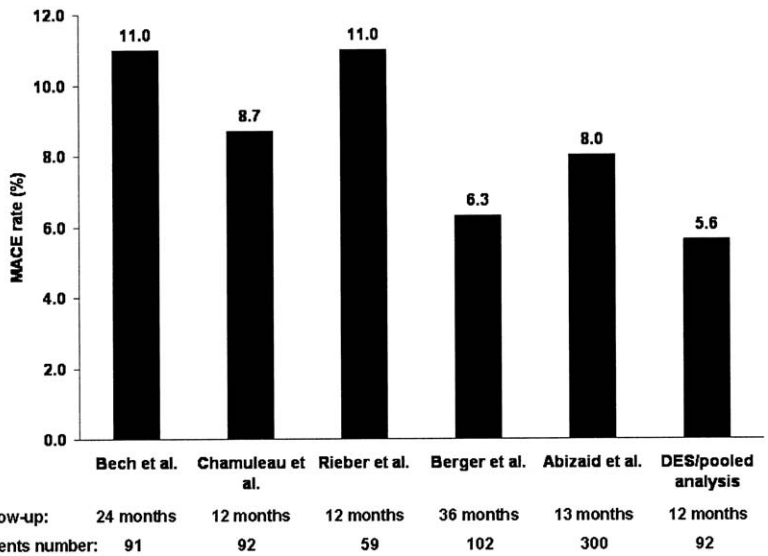

Figure 2. Rates of major adverse cardiac events (MACE) in patients with intermediate lesions in studies in which intervention was deferred based on physiologic lesion assessment (fractional flow reserve ≥0.75) or intravascular ultrasound analysis (minimal cross-sectional area >4.0 mm^2) (7–11) vs. the current pooled analysis of drug-eluting stent (DES)-treated patients from four randomized trials.

studied 71 patients with intermediate lesions in which PCI was deferred based on FFR ≥0.75. In 8% of patients TLR was required at a mean follow-up of 318 days. Among the subset of patients with an elevated C-reactive protein (>5.0 mg/l), the TLR rate was 27.8%, with most events occurring within six months. In patients requiring TLR, the mean diameter stenosis increased from 46.1% at baseline to 62.0% at follow-up (22).

Important data have also recently emerged describing a nonuniform spatial distribution of coronary thrombosis resulting in ST-segment elevation MI, with propensity for plaque rupture in the proximal segments of coronary arteries (24). Intermediate lesions located in these zones might represent a potential substrate for preventive intervention using DES. Thus, mounting evidence supports the necessity for sophisticated focal and regional approaches to identify segments of the coronary tree vulnerable to plaque progression and rupture. The present study suggests that DES implantation may possess the requisite safety and efficacy profile to consider plaque stabilization in such coronary segments. No doubt, the risk of late stent thrombosis and the requirement in extended combined antithrombotic therapy including aspirin and thienopyridine after DES implantation should be carefully weighed in deciding to use DES to treat an intermediate lesion.

Study limitations. The present post hoc analysis was not prespecified, and should therefore be considered as hypothesis generating. Inherently to all pooled analyses, the four trials differed somewhat in design, inclusion/exclusion criteria, stent design, and antiproliferative agents. Two different laboratories performed the QCA analyses. Nonetheless, the majority of baseline clinical and angiographic characteristics of the patients from the four trials were similar, and there was no evidence of statistical heterogeneity of the treatment effect in outcomes across the studies after adjustment for baseline clinical and angiographic characteristics. The study sample of 167 patients is modest, with even fewer patients undergoing angiographic follow-up; larger studies would be required to narrow the efficacy point estimates and to define if the usage of platelet glycoprotein IIb/IIIa inhibitors may further reduce ischemic clinical events in patients with intermediate lesions. However, it is unlikely that future randomized trials of DES versus BMS in intermediate lesions will be performed. Angiographic follow-up was available for only 65.9% of the patients; therefore, the precise rates of restenosis may differ from those reported in this study. Information on inducible ischemia, physiologic lesion assessment, and inflammatory biomarkers was not available in these studies; it would have been useful to further characterize the patients and lesions. Finally, the operators believed the treated lesions to be of sufficient clinical relevance to require treatment. Therefore, the results of this analysis cannot directly be extrapolated to lesions of lesser severity or to lesions requiring greater stent length. Moreover, it is unknown what percentage of the lesions treated in the present study were thin-capped fibroatheromas, and as such further studies are required to demonstrate the safety and efficacy of DES implantation in truly vulnerable plaques.

Conclusions. The current study suggests that the use of DES to treat intermediate lesions is safe and is associated with very low rates of early and one-year MACE. Prospective studies are therefore warranted to examine the benefits of DES compared to deferred intervention and maximal medical therapy in patients with intermediate stenoses of borderline hemodynamic significance, which may be prone to symptomatic progression, and in potentially vulnerable atheroma prone to plaque rupture resulting in acute coronary syndromes or sudden death.

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