Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 56, No. 19, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.08.608

EXPEDITED PUBLICATION

Selection Criteria for Drug-Eluting Versus Bare-Metal Stents and the Impact of Routine Angiographic Follow-Up

2-Year Insights From the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) Trial

Gregg W. Stone, MD,* Helen Parise, ScD,* Bernhard Witzenbichler, MD,† Ajay Kirtane, MD,* Giulio Guagliumi, MD,‡ Jan Z. Peruga, MD,§ Bruce R. Brodie, MD,‖ Dariusz Dudek, MD,¶ Martin Möckel, MD,# Alexandra J. Lansky, MD,* Roxana Mehran, MD*

New York, New York; Berlin, Germany; Bergamo, Italy; Lodz and Krakow, Poland; and Greensboro, North Carolina

Objectives We sought to identify patients with ST-segment elevation myocardial infarction most likely to benefit from drug-eluting stents (DES), and to evaluate the impact of routine angiographic follow-up on the apparent differences between stent types.

Background DES might have greatest utility in patients who would benefit most from their antirestenotic properties.

Methods We randomly assigned 3,006 patients with ST-segment elevation myocardial infarction to paclitaxel-eluting stents (PES) or to bare-metal stents (BMS). Events were assessed at 12 months and 24 months, with a subset undergoing routine angiographic follow-up at 13 months. Using well-known risk factors for restenosis and target lesion revascularization (TLR), risk groups were formed to examine the absolute differences between PES and BMS.

Results Compared with BMS, PES reduced TLR at 12 months from 7.4% to 4.5% ($p = 0.003$). Insulin-treated diabetes mellitus (hazard ratio: 3.12), reference vessel diameter ≤3.0 mm (hazard ratio: 2.89), and lesion length ≥30 mm (hazard ratio: 2.49) were independent predictors of 12-month TLR after BMS. In patients with 2 or 3 of these baseline risk factors, PES compared with BMS markedly reduced 12-month TLR (19.8% vs. 8.1%, $p = 0.003$). In patients with 1 of these risk factors, the 12-month rates of TLR were modestly reduced by PES (7.3% vs. 4.3%, $p = 0.02$). The 12-month TLR rates were low and similar for both stents in patients with 0 risk factors (3.3% vs. 3.2%, $p = 0.93$). Routine 13-month angiographic follow-up resulted in a marked increase in TLR procedures (more so with BMS) so that the absolute incremental benefit of PES compared with BMS doubled from 2.9% at 12 months to 6.0% at 24 months, a difference evident in all risk strata.

Conclusions Patients at high risk for TLR after BMS in ST-segment elevation myocardial infarction for whom DES are of greatest benefit may be identified. Conversely, DES may be of less clinical benefit for patients at lower risk for TLR after BMS. Routine angiographic follow-up increases the perceived clinical benefits of DES, and must be avoided to accurately estimate absolute treatment effects. (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI]; NCT00433966) (J Am Coll Cardiol 2010;56:1597–604) © 2010 by the American College of Cardiology Foundation

*From the Columbia University Medical Center/New York-Presbyterian Hospital and the Cardiovascular Research Foundation, New York, New York; †Charité Campus Benjamin Franklin, Berlin, Germany; ‡Ospedali Riuniti di Bergamo, Bergamo, Italy; §Medical University, Lodz, Poland; ‖LeBauer Cardiovascular Research Foundation and Moses Cone Hospital, Greensboro, North Carolina; ¶Jagiellonian University, Krakow, Poland; and #Charité Campus Virchow-Klinikum, Berlin, Germany. Dr. Stone has served on the scientific advisory board for Boston Scientific and Abbott Vascular, and has received honoraria from BMS-Sanofi, AstraZeneca, and The Medicines Company. Dr. Witzenbichler has received lecture honoraria from The Medicines Company and Boston Scientific. Dr. Kirtane has served as a consultant to Abbott Vascular, Boston Scientific, and Medtronic. Dr. Guagliumi has received consulting fees from Boston Scientific, lecture honoraria from The Medicines Company and Medtronic, and grant support from Medtronic, Boston Scientific, and Labcoat. Dr. Brodie is on the Speakers' Bureau for The Medicines Company and Medtronic. Dr. Dudek has received consulting and lecture honoraria from Abbott, Adamed, Biotronik, Balton, Bayer, BBraun, BioMatrix, Boston Scientific, Boehringer Inc., Bristol-Myers Squibb, Cordis, Cook, Eli Lilly, EuroCor, Glaxo, Invatec, Medtronic, The Medicines Company, MSD, Nycomed, Orbus-Neich, Pfizer, Possis, Promed, Sanofi-Aventis, Siemens, Solvay,

JACC Vol. 56, No. 19, 2010
November 2, 2010:1597–604

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
RVD = reference vessel diameter
STEMI = ST-segment elevation myocardial infarction
TLR = target lesion revascularization

Numerous randomized trials have reported that drug-eluting stents (DES), compared with bare-metal stents (BMS), reduce recurrent ischemia requiring repeat target lesion revascularization (TLR) procedures in patients with evolving ST-segment elevation myocardial infarction (STEMI) who are undergoing primary percutaneous coronary intervention (PCI) (1). However, most of these studies enrolled a small to moderate number of patients, and the performance of protocol-specified routine angiographic follow-up before or at the time of clinical end point assessment may have resulted in the performance of additional TLR procedures that would not otherwise have occurred had standard clinical indications for angiographic follow-up been followed (2–6), potentially overestimating the benefits of DES.

In contrast, in the large-scale, international HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial, the 12-month benefit of DES compared with BMS was modest (7). This trial was unique in that angiographic follow-up was planned at 13 months, only after assessment of the primary 12-month clinical end point (8). Two-year follow-up in the HORIZONS-AMI trial is now completed, permitting an evaluation of the impact of routine angiographic follow-up on the absolute and relative benefits of DES compared with BMS in STEMI. Moreover, physicians performing primary PCI are routinely faced with the decision of whether to use DES or BMS, with wide variability reported for DES utilization in STEMI. We hypothesize that the advantages of DES compared with BMS (before routine angiographic follow-up) would be most apparent for patients at high risk of clinical recurrence after BMS, whereas DES may offer minimal or no advantages to patients at low risk of recurrence after BMS. Therefore, we examined the 2-year results from the HORIZONS-AMI trial to develop selection criteria for DES versus BMS in STEMI, and to explore the impact of routine angiographic follow-up.

Methods

Patients and trial design. The trial design and 1-year results of the HORIZONS-AMI trial have been previously described (7,8). In brief, 3,602 patients ≥18 years old presenting within 12 h of symptom onset with ≥1 mm ST-segment elevation in ≥2 contiguous leads, or new left bundle branch block, or true posterior MI were enrolled and randomly assigned equally to unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor or to bivalirudin alone. Emergent coronary angiography with left ventriculography was then performed, followed by randomization of an additional 3,006 eligible patients in a 3:1 ratio to the TAXUS Express paclitaxel-eluting stent (PES) versus an otherwise identical Express BMS (both Boston Scientific, Natick, Massachusetts). Anatomic eligibility for stent randomization required a visually estimated reference vessel diameter (RVD) ≥2.25 and ≤4.0 mm, without excessive tortuosity or severe calcification. Angiographic exclusion criteria consisted of the following: planned unprotected left main stenting; a bifurcation lesion requiring planned stent implantation in both the main vessel and side branch; >100 mm stent length anticipated; infarction due to stent thrombosis; or anticipated bypass graft surgery within 30 days.

Aspirin, 324 mg chewed or 500 mg intravenously, was given in the emergency room, followed by 300 to 325 mg orally daily during the hospitalization and 75 to 81 mg daily indefinitely thereafter. A clopidogrel loading dose (either 300 or 600 mg, at investigator discretion) was administered before catheterization, followed by 75 mg orally daily for at least 6 months (1 year or longer recommended).

Clinical and angiographic follow-up. Clinical follow-up was planned at 30 days, 6 months, and 12 months, and then yearly for 5 years total. The primary clinical end points of the stent randomization arm were pre-specified at 12 months. Routine angiographic follow-up at 13 months (after ascertainment of the primary 12-month clinical end points) was pre-specified for 1,800 randomized stent patients in whom acute stent implantation was successful (diameter stenosis <10%, with TIMI [Thrombolysis In Myocardial Infarction] flow grade 3, and National Health, Lung, and Blood Institute type A or less persistent dissection) and in whom neither stent thrombosis occurred nor was bypass graft surgery performed within 30 days. Patients in the angiographic follow-up cohort with documented restenosis before 13 months, or with clinically driven angiography after 6 months but before 13 months, were also considered to have met the angiographic follow-up requirement.

Study end points. The trial was powered to demonstrate the superiority of PES over BMS for the reduction of 12-month ischemia-driven TLR, and noninferiority between the 2 stent types for the 12-month composite safety measure of major adverse cardiovascular events consisting of death, reinfarction, stroke, or stent thrombosis (7,8). The component definitions of major adverse cardiovascular events have been previously defined (8). TLR was considered ischemia-driven if the target lesion diameter stenosis was ≥50% with either a positive functional study, ischemic electrocardiographic changes, or symptoms referable to the target lesion, or ≥70% by core laboratory quantitative

Terumo, and Tyco. Dr. Möckel has received consulting and lecture honoraria from The Medicines Company. Dr. Lanksy has received research support from Boston Scientific and The Medicines Company. Dr. Mehran reports having received consulting fees from Bristol-Myers Squibb/Sanofi, Medtronic, and The Medicines Company. All other authors have reported that they have no relationships to disclose.

Manuscript received August 20, 2010; accepted August 26, 2010.

coronary analysis in the absence of documented ischemia. Stent thrombosis was defined according to the Academic Research Consortium classification (9). An independent clinical events committee blinded to treatment assignment adjudicated all primary end point events using original source documents and procedural angiograms. Independent core angiographic laboratory analysis was performed by technicians blinded to treatment assignment and clinical outcomes using validated methods (10).

Statistical analysis. Patients were analyzed according to randomized assignment, regardless of treatment received. Categorical outcomes were compared by the chi-square test or Fisher exact test. Continuous variables were compared by the Wilcoxon rank-sum test. Adverse event analyses were performed using time-to-event data, are displayed using Kaplan-Meier methodology, and were compared with the log-rank test.

Numerous prior studies have established that long lesions, small vessels, and insulin-treated diabetes mellitus are among the most consistent and widely accepted baseline risk factors for clinical and angiographic restenosis (11–16). Therefore, we created low-, intermediate-, and high-risk groups for restenosis using 3 variables. We assigned 1 point to each of 3 conditions: 1) RVD ≤3.0 mm; 2) lesion length ≥30 mm; and 3) insulin-treated diabetes. Patients with 0, 1, and ≥2 of these 3 risk factors were defined as being at low, intermediate, or high risk for TLR and restenosis, respectively. Outcomes by randomized treatment assignment (PES vs. BMS) were then assessed on the basis of strata of the risk score. Interaction testing was performed to determine the effect of low-risk versus high-risk strata on the difference in 12-month TLR between BMS and PES.

Results

Patients and 1-year outcomes. The baseline features of the randomized groups were well matched, except that current cigarette use was slightly more frequent among BMS patients, whereas lesion length was greater among PES patients (Table 1). As previously reported (7), compared with BMS, PES significantly reduced the 12-month rates of TLR, from 7.4% to 4.5% ($p = 0.003$), with nonsignificant differences in death, reinfarction, and stent thrombosis (Table 2).

Angiographic follow-up was completed in 1,203 patients, including 193 patients with recurrent ischemia in whom angiographic end point criteria were met before the routine 13-month angiogram, and 1,010 patients in whom a follow-up angiogram was performed at 13 months for protocol purposes. As previously reported (7), binary angiographic restenosis was present in 76 of 328 lesions (23.2%) in 293 patients in the BMS group versus 103 of 1,066 lesions (9.7%) in 910 patients in the PES group ($p < 0.0001$).

Table 1 Baseline Characteristics According to Stent Randomization

Characteristic	BMS (n = 749)	PES (n = 2,257)	p Value
Clinical features			
Age, yrs	59.3 (26.0–89.0)	59.9 (30.9, 92.3)	0.26
Male	569 (76.0)	1,738 (77.0)	0.56
Diabetes mellitus	114 (15.2)	364/2,256 (16.1)	0.55
Insulin-treated diabetes mellitus	31 (4.1)	98/2,256 (4.3)	0.92
Hypertension	389 (51.9)	1,155/2,256 (51.2)	0.73
Hyperlipidemia	308 (41.1)	953/2,256 (42.2)	0.59
Current smoker	388/748 (51.9)	1041/2,246 (46.3)	0.009
Symptom onset to balloon, min	97 (71, 138)	100 (74–134)	0.92
Killip class 2–4	60/748 (8.0)	199/2,254 (8.8)	0.50
Renal insufficiency*	107/696 (15.4)	328/2,102 (15.6)	0.88
Angiographic features			
Number of lesions treated (mean per patient)	820 (1.1 ± 0.4)	2,527 (1.1 ± 0.4)	0.12
Infarct lesion = left anterior descending	347/820 (42.3)	1,008/2,527 (39.9)	0.22
Baseline TIMI flow per vessel†			
0/1	442/770 (57.4)	1424/2,348 (60.6)	0.11
2	117/770 (15.2)	320/2,348 (13.6)	0.28
3	211/770 (27.4)	604/2,348 (25.7)	0.36
Reference vessel diameter, mm†	2.90 ± 0.50	2.89 ± 0.51	0.75
Reference vessel diameter ≤3.0, mm†	436/741 (58.5)	1,332/2,228 (59.8)	0.65
Minimal luminal diameter, mm†	0.35 ± 0.45	0.35 ± 0.45	0.81
Diameter stenosis, %†	87.4 ± 15.4	87.6 ± 15.4	0.83
Lesion length, mm†	16.2 ± 8.8	17.5 ± 10.1	0.006
Total lesion length ≥30 mm (%)†	104/735 (14.1)	434/2,209 (19.6)	0.0008

Values are median (range), n (%), median (IQR), or mean ± SD. *Denotes baseline creatinine clearance calculated using the Cockcroft-Gault equation <60 ml/min. †Denotes core laboratory assessment.

BMS = bare-metal stent(s); IQR = interquartile range; PES = paclitaxel-eluting stent(s); TIMI = Thrombolysis In Myocardial Infarction.

JACC Vol. 56, No. 19, 2010
November 2, 2010:1597–604

Table 2 Clinical Outcomes at 12 Months According to Stent Randomization

Outcome	BMS (n = 749)	PES (n = 2,257)	p Value
Ischemia-driven TLR	7.4% (54)	4.5% (100)	0.003
Ischemia-driven TVR	8.8% (64)	5.9% (129)	0.006
Death, all-cause	3.5% (26)	3.5% (78)	0.97
Cardiac	2.7% (20)	2.4% (54)	0.67
Noncardiac	0.8% (6)	1.1% (24)	0.55
Reinfarction	4.5% (33)	3.7% (81)	0.31
Q-wave	1.9% (14)	2.0% (45)	0.83
Non–Q-wave	2.6% (19)	1.8% (39)	0.16
Stent thrombosis, any	3.4% (25)	3.1% (69)	0.72
ARC definite	3.0% (22)	2.7% (59)	0.65
ARC probable	0.4% (3)	0.5% (10)	0.87

Values are presented as Kaplan-Meier estimates (number of events).
ARC = Academic Research Consortium; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

Risk groups for target lesion revascularization. All 3 risk variables (lesion length ≥30 mm, RVD ≤3.0 mm, and insulin-requiring diabetes) were independent correlates of 12-month TLR after BMS (Table 3). Among patients with 0, 1, or ≥2 risk factors, the 12-month rates of TLR with BMS ranged from 3.3% (low risk) to 19.8% (high risk) ($p_{trend} < 0.0001$). As shown in the top graph of Figure 1, PES markedly reduced the 12-month rates of TLR in the patient group at highest risk for TLR after BMS (2 or 3 risk factors), modestly reduced 12-month TLR in the intermediate-risk group (1 risk factor), but did not reduce TLR in the patient group at low risk for TLR after BMS (0 risk factor). Formal interaction testing demonstrated a significant effect of high-risk versus low-risk strata on the difference in the 12-month rates of TLR between PES and BMS (p = 0.02). PES did significantly reduce the 13-month rates of angiographic restenosis in all 3 groups, regardless of baseline risk for TLR after BMS (Fig. 1B).

The 12-month rates of cardiac death, reinfarction, and stent thrombosis were higher among patients at high risk for TLR after BMS than among patients at intermediate risk and low risk for TLR after BMS (Fig. 2). The rates of cardiac death, reinfarction, and stent thrombosis at 12 months were comparable among low and intermediate TLR risk patients treated with PES versus BMS (Figs. 2A and 2B), whereas among patients at high risk for BMS TLR, the 12-month rates of cardiac death and stent thrombosis tended to be less with PES, although these differences did not reach statistical significance (Fig. 2B).

Table 3 Multivariable Predictors of 12-Month Ischemic Target Lesion Revascularization Among Patients Randomized to Bare-Metal Stents

Variable	HR (95% CI)	p Value	Weighted Score
Insulin-treated diabetes mellitus	3.12 (1.23–7.87)	0.02	1
Baseline RVD ≤3.0 mm	2.89 (1.56–5.34)	0.0007	1
Total lesion length ≥30 mm	2.49 (1.33–4.68)	0.004	1

Model c-statistic = 0.66.
CI = confidence interval; HR = hazard ratio; RVD = reference vessel diameter.

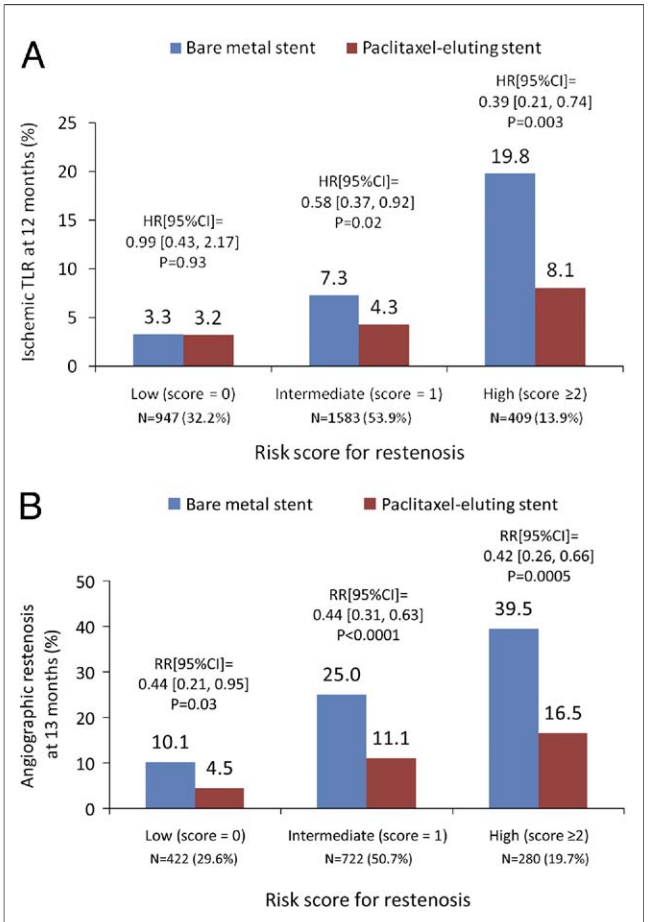

Figure 1 Rates of 12-Month TLR and 13-Month Angiographic Restenosis

(A) Rates of 12-month ischemic target lesion revascularization (TLR) and **(B)** 13-month angiographic restenosis in patients randomly allocated to paclitaxel-eluting stents **(red bars)** or to bare-metal stents **(blue bars)** according to the risk strata for restenosis. CI = confidence interval; HR = hazard ratio; RR = relative risk.

2-year clinical outcomes. As shown in Figure 3, the Kaplan-Meier curves for ischemic TLR favoring PES over BMS spread significantly between 3 months and 6 months, and then slightly between 6 months and 12 months. Coincident with the 13-month angiographic follow-up, however, there was a sharp increase in ischemic TLR in both groups (although more so with BMS), followed by the curves again becoming parallel between 14 months and 24 months. Underlying this finding, among the 1,010 patients with 1,204 lesions in whom the 13-month angiogram was performed for protocol purposes only, binary angiographic restenosis was present in 132 lesions (11.0%), including 60 of 276 BMS-treated lesions and 72 of 928 PES-treated lesions (21.7% vs. 7.8%, respectively; p < 0.0001). As a result, TLR within 30 days of this protocol-based angiogram was performed in 84 patients (8.3%), including 33 of 239 BMS patients and 51 of 771 PES patients (13.8% vs. 6.6%, respectively; p = 0.0004), and rarely thereafter (Fig. 4).

Cumulative event rates at 24 months and incremental event rates between 12 months and 24 months appear in Table 4. Compared with BMS, the absolute difference (95% confidence interval) in TLR favoring PES rose from 2.9% (0.8% to 5.0%) at 12 months to 6.0% (3.1% to 8.8%) at 24 months, and the hazard ratio for the benefit of PES was marginally improved (hazard ratio: 0.61 [95% confidence interval (CI): 0.44 to 0.84], p = 0.003 at 12 months, and 0.57 [95% CI: 0.44 to 0.72], p < 0.0001 at 24 months).

Finally, Figure 5 shows the rates of ischemic TLR at 24 months among the randomized PES and BMS stratified in the low-, intermediate-, and high-risk groups for BMS TLR. Compared with BMS, the absolute benefit of PES was greater in all 3 groups at 24 months (Fig. 5) compared with 12 months (Fig. 1A), and the reductions in TLR at 24 months with PES were highly significant in the intermediate-risk and high-risk strata.

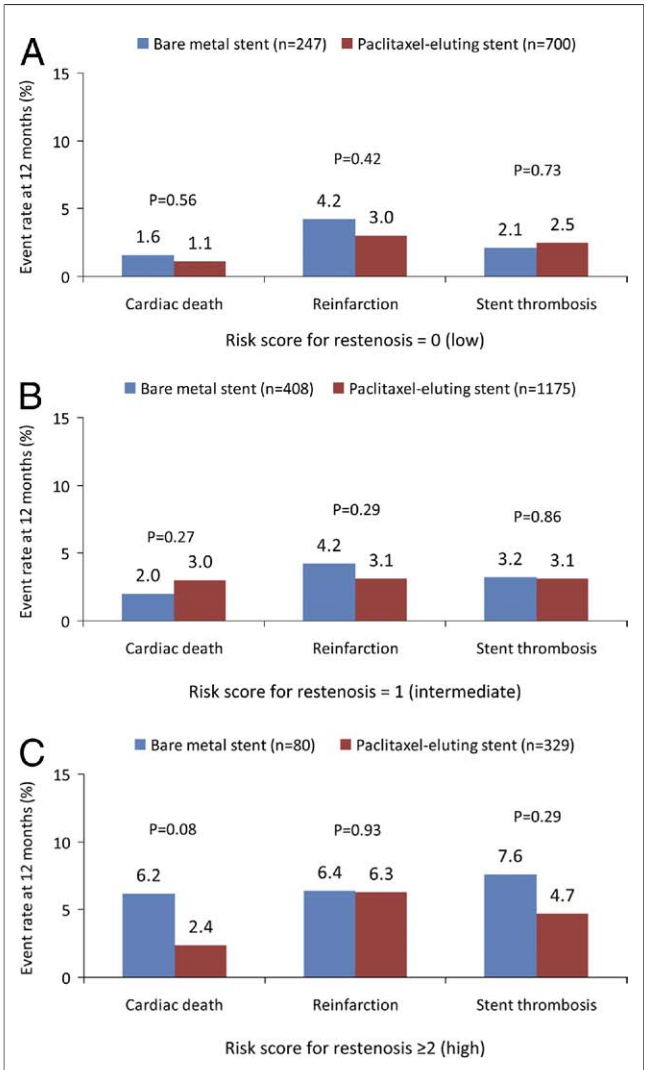

Figure 2 **Rates of Cardiac Death, Reinfarction, and ARC Stent Thrombosis**

Rates of cardiac death, reinfarction, and Academic Research Consortium (ARC) definite or probable stent thrombosis at 12 months among patients randomly assigned to paclitaxel-eluting stents **(red bars)** or to bare-metal stents **(blue bars)** according to the risk strata for restenosis. **(A)** Patients at low risk for restenosis; **(B)** patients at intermediate risk for restenosis; and **(C)** patients at high risk for restenosis.

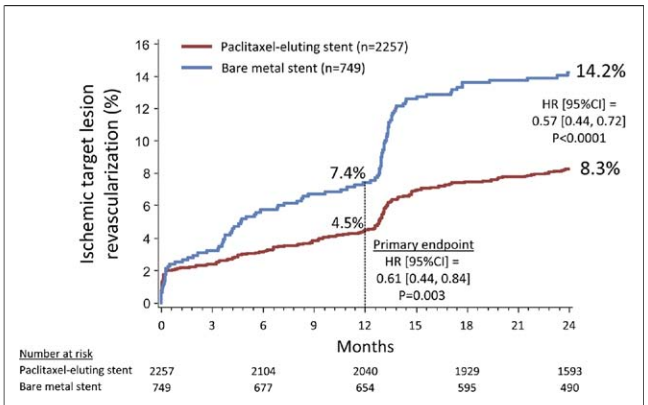

Figure 3 **Time-to-Event Curves Through 24 Months for Ischemia-Driven TLR**

Time-to-event curves through 24 months for ischemia-driven target lesion revascularization (TLR) among patients randomly assigned to paclitaxel-eluting stents **(red line)** or to bare-metal stents **(blue line)**. The **vertical dotted line** represents the timing of the primary clinical end point at 12 months. Routine protocol-driven angiographic follow-up was performed at 13 months in 1,010 of the 3,006 (33.6%) randomized patients. Abbreviations as in Figure 1.

Discussion

The principal findings from this report are that: 1) a simple risk model incorporating the 3 most widely accepted baseline risk factors for restenosis was created that was capable of differentiating patients at low, intermediate, and high risk for ischemia-driven TLR within 12 months after BMS

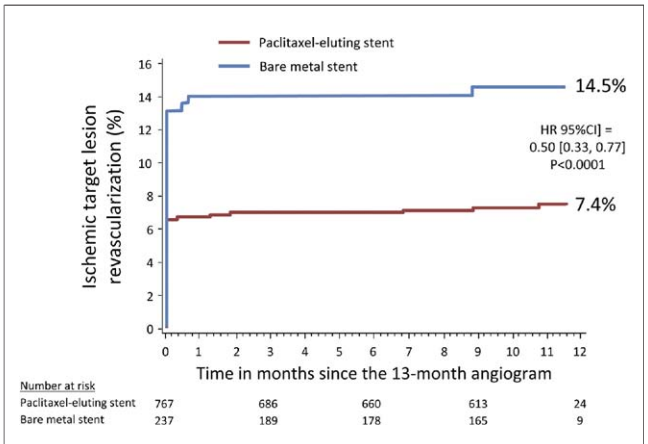

Figure 4 **Landmark Analysis for TLR From Angiographic Follow-Up**

Landmark analysis for the occurrence of target lesion revascularization (TLR) from the time of protocol-specified routine angiographic follow-up at 13 months in 1,004 patients. Note that 6 patients who had a previous TLR procedure were excluded from this cohort. **Blue line** = bare-metal stent; **red line** = paclitaxel-eluting stent.

JACC Vol. 56, No. 19, 2010
November 2, 2010:1597–604

Table 4 Clinical Outcomes at 24 Months According to Stent Randomization

Outcome	Incremental Events Between 12 and 24 Months			Cumulative Events Between 0 and 24 Months		
	BMS (n = 749)	PES (n = 2,257)	p Value	BMS (n = 749)	PES (n = 2,257)	p Value
Ischemia-driven TLR	8.5% (58)	5.4% (113)	0.003	14.2% (101)	8.3% (178)	<0.0001
Ischemia-driven TVR	8.5% (58)	5.4% (113)	0.003	16.6% (118)	11.0% (236)	<0.0001
Death, all-cause	1.9% (13)	0.9% (18)	0.03	5.3% (39)	4.3% (96)	0.27
Cardiac	0.6% (4)	0.3% (6)	0.26	3.3% (24)	2.7% (60)	0.43
Noncardiac	1.3% (9)	0.6% (12)	0.053	2.2% (15)	1.7% (36)	0.44
Reinfarction	1.5% (10)	2.3% (48)	0.19	6.0% (43)	5.7% (123)	0.74
Stent thrombosis, any	0.7% (5)	1.1% (23)	0.41	4.1% (30)	4.1% (90)	0.99
ARC definite	0.6% (4)	1.1% (22)	0.27	3.6% (26)	3.7% (79)	0.97
ARC probable	0.1% (1)	0.0% (1)	0.41	0.6% (4)	0.5% (11)	0.88

Values are presented as Kaplan-Meier estimates (number of events).
Abbreviations as in Tables 1 and 2.

implantation in STEMI (ranging from 3.3% to 19.8%). 2) Among patients at highest risk for restenosis, PES resulted in a marked reduction in TLR at 12 months. Among patients at intermediate risk for restenosis, PES resulted in a modest but significant reduction in 12-month TLR. In contrast, no difference in TLR at 12 months was present between PES and BMS in patients at low risk for restenosis. Compared with the BMS, PES did significantly reduce angiographic restenosis in all 3 risk strata, however. 3) The performance of routine angiographic follow-up at 13 months triggered a sharp incremental increase in the number of TLR procedures compared with the background event rate that was occurring before angiography, more so with BMS than with PES. 4) As a result, the performance of routine angiographic follow-up after assessment of the primary 12-month clinical end point markedly increased the apparent absolute clinical benefits of PES, compared with BMS, at the 2-year time point, with differences apparent in all 3 risk groups.

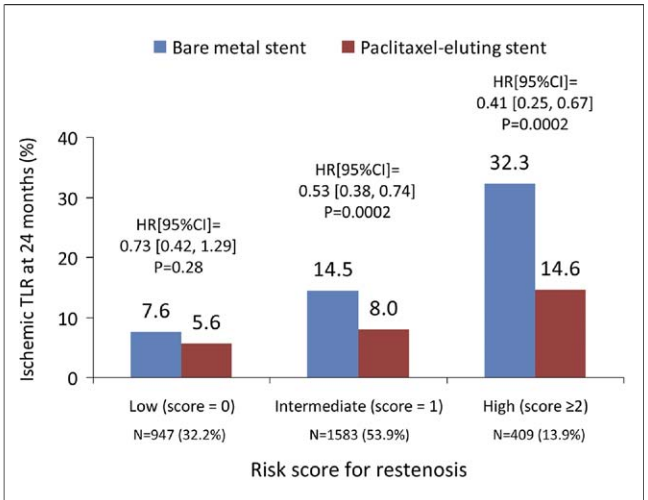

Figure 5 Rates of 24-Month Ischemic TLR

Rates of 24-month ischemic target lesion revascularization (TLR) for patients randomly allocated to either paclitaxel-eluting stents **(red bars)** or bare-metal stents **(blue bars)** according to the risk strata for restenosis. Abbreviations as in Figure 1.

If accurate assessments of novel therapies are to be obtained, estimates of the treatment effect must be examined under real-life conditions. Randomized trials may incorporate artificial study processes that may insidiously affect clinical event rates (2–6). In this regard, a meta-analysis of 11 randomized trials (3,607 total patients) of DES versus BMS in STEMI demonstrated a mean 7.6% reduction in target vessel revascularization with DES at 12 months (5.0% vs. 12.6%, respectively; $p < 0.0001$) (1). However, to characterize the vascular responses of the different stent types, routine angiographic follow-up was performed before assessment of the clinical end point in 8 of these 11 studies (1), likely increasing the absolute if not the relative benefit of DES by triggering TLR procedures in asymptomatic patients who otherwise would not have undergone angiography (the "oculostenotic reflex") (2–6).

The HORIZONS-AMI study is the largest prospective, randomized, controlled trial of primary stenting in STEMI, and to our knowledge the first large-scale trial in any setting to intentionally schedule angiographic follow-up only after assessment of the primary clinical end point (7), allowing an accurate assessment of the treatment effect of DES in STEMI. In the HORIZONS-AMI trial, the absolute rates of clinically-driven TLR in both the BMS and PES arms at 12 months (7.4% and 4.5%, respectively), as well as the 2.9% difference favoring PES, were substantially lower than those reported from prior studies in which routine angiographic follow-up was common (1), although they were comparable to the 1-year results from the PASSION (Paclitaxel-Eluting Stent Versus Conventional Stent in Myocardial Infarction With ST-Segment Elevation) trial, in which routine angiographic follow-up was not performed after randomization of 619 STEMI patients to PES or to BMS (17).

Of note, as restenosis was more common with BMS than DES (even in asymptomatic patients), protocol-mandated routine angiographic follow-up in the HORIZONS-AMI

study triggered a greater proximate increase in TLR procedures in the BMS arm than in the PES arm, so that the absolute benefit of PES compared with BMS more than doubled from 1 to 2 years (2.9% vs. 6.0%). As a result, the 2-year estimates of PES clinical efficacy were likely inflated by this study-specific process, regardless of the baseline risk for TLR after BMS. In contrast, without angiographic follow-up in the PASSION study, the absolute benefit of PES compared with BMS in reducing TLR was stable between 1 and 2 years (2.5% vs. 3.2%, respectively) (17,18).

Moreover, 13-month routine angiographic follow-up was performed in only 33.6% of the HORIZONS-AMI trial stent-randomized patients. The results would have been even more skewed had routine angiographic follow-up been performed in a greater percentage of study participants. As seen in Figure 4, had all patients undergone routine angiographic follow-up (rather than only 33.6%), the absolute increase in TLR favoring PES over BMS from 1 to 2 years might have increased by as much as 7%, rather than the 3% observed. These findings serve as a stark illustration that routine follow-up angiography must be delayed until after the timing of the primary end point in all future randomized trials, or better yet, performed in a separate study.

Given the incremental cost of DES compared with BMS, and ongoing concerns of very late stent thrombosis (19,20), which may occur more frequently after DES implantation in a ruptured, thrombotic plaque (21,22), the use of DES in STEMI should be reserved for patients most likely to benefit. While this may seem evident, DES utilization rates in STEMI vary widely by center and operator. In a nonrandomized propensity-controlled study from Ontario, Tu et al. (23) reported that DES was associated with reduced rates of target vessel revascularization compared with BMS in patients with 2 or 3 risk factors for restenosis, including diabetes, vessels <3 mm in diameter, and lesions ≥ 20 mm in length, but not among lower risk patients. Few patients in this study had STEMI, however.

The present analysis, drawn from a carefully monitored, prospective. randomized large-scale international trial thus confirms and extends these findings to patients with STEMI, and to slightly lower risk patients for restenosis. A simple risk score using the baseline variables of insulin-treated diabetes, RVD ≤ 3.0 mm, and lesion length ≥ 30 mm effectively differentiated the clinical and angiographic utility of PES versus BMS after primary PCI. In the 14% of patients with a risk score of ≥ 2, PES resulted in an 11.7% absolute reduction in 12-month TLR (number needed to treat to prevent 1 TLR = 8.5), with nonsignificant trends toward less cardiac death and stent thrombosis. These data strongly support PES use in this group of patients. In the 54% of patients with 1 risk factor, a modest 3.0% absolute reduction in 12-month TLR was conferred by PES compared with BMS (number needed to treat to prevent 1 TLR = 33.3). Conversely, in the 32% of patients with a risk score of 0, PES and BMS had nearly identical rates of TLR at 12 months. Compared with BMS, PES significantly reduced angiographic restenosis in all 3 risk strata, although the absolute reduction in restenosis with PES varied according to baseline risk (number needed to treat to prevent 1 restenosis = 17.9, 7.2, and 4.3 in the low-, intermediate-, and high-risk groups, respectively). The decision whether to use PES in patients at intermediate or low risk for TLR after BMS should therefore be individualized, and may involve considerations such as the likelihood of prolonged adherence to dual antiplatelet therapy (24), whether future revascularization procedures are anticipated, and cost. Of note, by 2 years, the absolute reductions in TLR with PES compared with BMS were more pronounced in all 3 risk strata, although caution in the interpretation of the differences between stent types after 1 year is required, given the confounding effects from routine angiographic follow-up.

Study limitations. Several limitations of this study deserve discussion. First, the present results apply only to patients with STEMI, as well as to comparisons of PES versus BMS, and should not be generalized to different clinical scenarios or other DES with different risk-benefit profiles. Nonetheless, the analysis methodology described herein should be relevant to these other situations. Second, although diabetes, lesion length, and RVD have repeatedly been shown to be predictors of TLR after BMS in numerous clinical settings (and were similarly predictive in the present study), additional analysis from this and other datasets are warranted to identify whether additional risk factors for TLR after BMS in STEMI exist that could further strengthen the model. Third, the 13-month rates of angiographic follow-up varied in the 3 BMS risk groups, likely because of selection bias leading to greater re-study of patients at higher risk for restenosis. Fourth, while it is likely that most patients undergoing 13-month angiography did so for protocol purposes only, it is possible that progressive symptoms developed in a minority between the 12-month primary clinical end point assessment and the 13-month scheduled angiogram; the case report form did not make this distinction. Fifth, TLR procedures without evident ischemia were adjudicated as non–end points by the clinical event adjudication committee. However, a $\geq 70\%$ diameter stenosis by quantitative coronary angiography (equivalent to a $\geq 80\%$ to 90% visually estimated stenosis) was adjudicated as an ischemia-driven TLR because of its likelihood to cause an adverse event if untreated. While this definition is standard among DES studies, this complexity further highlights the intricacies of study interpretation after performing nonclinically indicated procedures such as routine angiographic follow-up. Finally, even the HORIZONS-AMI study was not powered to detect differences in low-frequency safety end points between stent types, such as death and stent thrombosis, especially within the 3 TLR risk groups created.

JACC Vol. 56, No. 19, 2010
November 2, 2010:1597–604

Conclusions

These limitations notwithstanding, the present study provides important guidance as to which patients might benefit from PES rather than BMS in STEMI. In patients at high risk for TLR after BMS, PES markedly reduces clinical and angiographic restenosis, with no safety concerns apparent. Conversely, the selection of stent type for patients at intermediate and low risk for TLR after BMS should be individualized, but may be considered as long as long-term dual antiplatelet therapy compliance is likely. Finally, routine angiographic follow-up in stent studies distorts the accurate assessment of clinical treatment effects and must be avoided in future randomized trials.

Reprint requests and correspondence: Dr. Gregg W. Stone, Columbia University Medical Center, New York-Presbyterian Hospital, The Cardiovascular Research Foundation, 111 East 59th Street, 11th Floor, New York, New York 10022. E-mail: gs2184@columbia.edu.

REFERENCES

1. De Luca G, Stone GW, Suryapranata H, et al. Efficacy and safety of drug-eluting stents in ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. Int J Cardiol 2009;133:213–22.
2. Rupprecht HJ, Espinola-Klein C, Erbel R, et al. Impact of routine angiographic follow-up after angioplasty. Am Heart J 1998;136:613–9.
3. Ruygrok PN, Melkert R, Morel M-AM, et al. Does angiography six months after coronary intervention influence management and outcome? J Am Coll Cardiol 1999;34:1507–11.
4. Pinto DS, Stone GW, Ellis SG, et al. Impact of routine angiographic follow-up on the clinical benefits of paclitaxel-eluting stents: results from the TAXUS-IV trial. J Am Coll Cardiol 2006;48:32–6.
5. ten Berg JM, Kelder JC, Suttorp MJ, Verheugt FWA, Thijs Plokker HW. Influence of planned six-month follow-up angiography on late outcome after percutaneous coronary intervention: a randomized study. J Am Coll Cardiol 2001;38:1061–9.
6. Uchida T, Popma J, Stone GW, et al. The clinical impact of routine angiographic follow-up in randomized trials of drug-eluting stents: a critical assessment of "oculostenotic" reintervention in patients with intermediate lesions. J Am Coll Cardiol Intv 2010;3:403–11.
7. Stone GW, Lansky AJ, Pocock SJ, et al. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. N Engl J Med 2009;360:1946–59.
8. Mehran R, Brodie B, Cox DA, et al. The Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial: study design and rationale. Am Heart J 2008;156:44–56.
9. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
10. Lansky A, Popma J. Qualitative and quantitative angiography. In: Topol EJ, editor. Textbook of Interventional Cardiology. Philadelphia, PA: WB Saunders, 1999:725–47.
11. Mercado N, Boersma E, Wijns W, et al. Clinical and quantitative coronary angiographic predictors of coronary restenosis. A comparative analysis from the balloon-to-stent era. J Am Coll Cardiol 2001;38:645–52.
12. Elezi S, Kastrati A, Pache J, et al. Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. J Am Coll Cardiol 1998;32:1866–73.
13. Singh M, Gersh BJ, McClelland RL, et al. Clinical and angiographic predictors of restenosis after percutaneous coronary intervention: insights from the Prevention of Restenosis With Tranilast and Its Outcomes (PRESTO) trial. Circulation 2004;109:2727–31.
14. Kastrati A, Schomig A, Elezi S, et al. Predictive factors of restenosis after coronary stent placement. J Am Coll Cardiol 1997;30:1428–36.
15. West NE, Ruygrok PN, Disco CM, et al. Clinical and angiographic predictors of restenosis after stent deployment in diabetic patients. Circulation 2004;109:867–73.
16. Cutlip DE, Chauhan MS, Baim DS, et al. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. J Am Coll Cardiol 2002;40:2082–9.
17. Laarman GJ, Suttorp MJ, Dirksen MT, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. N Engl J Med 2006;355:1105–13.
18. Vink MA. Five-year clinical follow-up of the PASSION trial: Primary PCI With a Paclitaxel-Eluting Stent vs. a Bare-Metal Stent in Acute ST-Elevation Myocardial Infarction. Late breaking trial presented at: American College of Cardiology, Annual Scientific Session/i2 Summit; March 16, 2010; Atlanta, GA. Available at: http://www.tctmd.com/Show.aspx?id=89146. Accessed May 6, 2010.
19. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 2007;356:998–1008.
20. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.
21. Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation 2008;118:1138–45.
22. de la Torre-Hernández JM, Alfonso F, Hernández F, et al. Drug-eluting stent thrombosis: results from the multicenter Spanish registry ESTROFA (Estudio Español sobre Trombosis de stents Farmacoactivos). J Am Coll Cardiol 2008;51:986–90.
23. Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in Ontario. N Engl J Med 2007;357:1393–402.
24. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. Circulation 2006;113:2803–9.

Key Words: acute myocardial infarction ■ angiography ■ bare-metal stent ■ drug-eluting stent ■ outcomes.