JACC: CARDIOVASCULAR INTERVENTIONS VOL. 5, NO. 10, 2012

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcin.2012.06.013

CLINICAL RESEARCH

Predictors of Early, Late, and Very Late Stent Thrombosis After Primary Percutaneous Coronary Intervention With Bare-Metal and Drug-Eluting Stents for ST-Segment Elevation Myocardial Infarction

Bruce Brodie, MD,* Yashashwi Pokharel, MD,† Ankit Garg, MD,† Grace Kissling, PHD,‡ Charles Hansen, MA,† Sally Milks, RN,* Michael Cooper, MD,* Christopher McAlhany, MD,* Tom Stuckey, MD*

Greensboro and Research Triangle Park, North Carolina

Objectives The purpose of this study was to evaluate the frequency and predictors of stent thrombosis (ST) after stenting for ST-segment elevation myocardial infarction (STEMI).

Background Stent thrombosis remains a major concern with STEMI patients treated with primary percutaneous coronary intervention.

Methods Consecutive patients (N = 1,640) undergoing stenting for STEMI were prospectively enrolled in our database and followed for 1 to 15 years. Bare-metal stents were implanted from 1995 to 2002, and drug-eluting and bare-metal stents were implanted from 2003 to 2009. Stent thrombosis was defined as definite or probable.

Results Our population had a high risk profile, including a high incidence of Killip class III to IV (11.5%) and STEMI due to ST (10.2%). Stent thrombosis occurred in 124 patients, including 42 with early ST (0 to 30 days), 35 with late ST (31 days to 1 year), and 47 with very late ST (>1 year). The frequency of ST was 2.7% at 30 days, 5.2% at 1 year, and 8.3% at 5 years. Independent predictors of early or late ST were STEMI due to ST (hazard ratio [HR]: 4.38, 95% confidence interval [CI]: 2.27 to 8.45), small stent size (HR: 2.44, 95% CI: 1.49 to 4.00), Killip class III to IV (HR: 2.39, 95% CI: 1.30 to 4.40), and reperfusion time ≤2 h (HR: 2.09, 95% CI: 1.03 to 4.24). Drug-eluting stent was the only independent predictor of very late ST (HR: 3.73, 95% CI: 1.81 to 7.88).

Conclusions Stent thrombosis after primary percutaneous coronary intervention is relatively frequent and continues to increase out to 5 years. New strategies are needed to prevent ST in STEMI patients, and targeted therapies are needed in patients identified at highest risk. (J Am Coll Cardiol Intv 2012;5:1043–51) © 2012 by the American College of Cardiology Foundation

From *The LeBauer Cardiovascular Research Foundation, Greensboro, North Carolina; †Internal Medicine Residency Program, Moses H. Cone Memorial Hospital, Greensboro, North Carolina; and the ‡National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. This study was supported by an unrestricted grant from the LeBauer Charitable Research Foundation and by the Intramural Research Program of the National Institutes of Health, National Institute of Environmental Health Sciences (Z01ES045005). Dr. Brodie has served on the Speakers' Bureau for the Medicines Company and Medrad/Possis. Dr. Stuckey has served as consultant to and on the Speakers' Bureau and on the Advisory Board for Boston Scientific Corporation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 6, 2012; revised manuscript received May 21, 2012, accepted June 21, 2012.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 5, NO. 10, 2012
OCTOBER 2012:1043–51

The use of coronary stents has become the preferred therapy with primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI). This is based on data showing that stents have been able to reduce ischemic-driven target vessel revascularization and angiographically documented restenosis and re-occlusion (1,2). Unfortunately, stent thrombosis (ST) is more frequent after stenting for STEMI than after elective stenting with both drug-eluting stents (DES) and bare-metal stents (BMS) (3–7). Data from the Thoraxcenter Registry have shown significantly higher ST rates at 3 years after stenting for STEMI versus elective stenting (3.3% vs. 1.1%, p = 0.0009), and data from both the Thoraxcenter Registry and the SCAAR registry (Swedish Coronary Angiography and Angioplasty Registry) have shown higher adjusted rates of ST after stenting for STEMI versus elective stenting (adjusted hazard ratio [HR]: 3.10, 95% confidence interval [CI]: 1.80 to 5.34, and HR: 2.57, 95% CI: 1.82 to 3.62, respectively) (6,7). The HORIZONS-AMI (Harmonizing Outcomes with RevascularIZatiON and Stents in Acute Myocardial Infarction) trial found a high frequency of ST with both DES and BMS at 3 years (4.8% vs. 4.3%, p = 0.68), which was associated with a high incidence of reinfarction (71.8%) and short-term mortality (16.0%) (8,9). Although this trial did not show any difference in the frequency of ST between DES and BMS, there is still concern that very late ST (>1 year) might be more frequent with DES than BMS, because of increased frequency of late stent malapposition and poor healing of DES after primary PCI (10–12). For all these reasons, ST after stenting for STEMI has been a major concern.

See page 1052

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
GPI = glycoprotein IIb/IIIa platelet inhibitor
HR = hazard ratio
MI = myocardial infarction
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
RT = reperfusion time
ST = stent thrombosis
STEMI = ST-segment elevation myocardial infarction

We have prospectively enrolled STEMI patients treated with primary PCI into an ongoing database dating back to the early use of stents with STEMI in 1995. This has allowed for long-term follow-up and has provided a unique opportunity to evaluate early, late, and very late ST. The purpose of this study is to evaluate the frequency and predictors of early, late, and very late ST after stenting for STEMI.

Methods

Study population. The study population consists of 1,640 consecutive patients with STEMI treated with primary PCI at our institution from 1995 through 2009 who received a stent or who had STEMI due to ST. Patients were included in our registry if they had electrocardiographic ST-segment elevation ≥1 mm in ≥2 contiguous leads or new left bundle branch block, symptoms of <12-h duration (>12 h for persistent ischemic symptoms or hemodynamic compromise), and were treated with primary PCI.

Treatment protocol. Patients were treated with contemporary standards of care for primary PCI. In the early years, this included aspirin, unfractionated heparin, and glycoprotein IIb/IIIa platelet inhibitors and, in very recent years, included aspirin and bivalirudin, usually without glycoprotein IIb/IIIa platelet inhibitors. Ticlopidine (in the early years) or clopidogrel were given immediately before or at the time of PCI. Bare-metal stents were used exclusively from 1995 to 2003, and DES or BMS were used from 2003 to 2009 at the discretion of the operator. Of 410 patients who received DES, 366 stents were first-generation DES (sirolimus-eluting, paclitaxel-eluting, or zotarolimus-eluting stents), and 44 were second-generation stents (everolimus-eluting stents).

Data collection, clinical follow-up, and definitions. Patients were enrolled prospectively into the database from 1995 through 2009. Procedural data were assessed and entered by the interventional cardiologist at the time of the PCI, and hospital outcomes were assessed from chart reviews on an ongoing basis. Follow-up events were obtained from reviews of medical records and telephone contact every year. Medical records for each patient were reviewed to identify all readmissions for acute coronary syndromes and all readmissions resulting in mortality.

Stent thrombosis was defined as definite or probable ST according to the Academic Research Consortium (ARC) definition (13). Definite ST occurred when there was an acute coronary syndrome with angiographic confirmation of thrombus within the stent with partial or total occlusion of the stent. Probable ST occurred when there was an infarct in the territory of the stented vessel without angiographic confirmation or when there was unexplained sudden death within 30 days. Early ST was defined as ST occurring from 0 to 30 days, late ST was defined as ST occurring from 31 days to 1 year, and very late ST was defined as ST occurring after 1 year.

Stent type was classified as DES if a new DES was implanted and as BMS if a new BMS was implanted with the primary PCI for STEMI. In patients who had STEMI due to ST in whom no new stent was implanted, stent type was classified as DES or BMS depending on the type of stent originally implanted.

Statistical analyses. Statistical comparisons of categorical variables were performed with the chi-square or Fisher exact test, as appropriate. Frequencies of stent thromboses were assessed by Kaplan-Meier estimates at 30 days, 1 year, and 5 years, and comparisons of frequencies in patients with and without selected variables were made with log-rank statistics. Landmark analyses were performed to compare frequencies of late

ST (31 days to 1 year) and very late ST (>1 to 5 years) in patients with and without selected variables. Patients who survived for 30 days without ST were included in landmark analyses for late ST, and patients who survived for 1 year without ST were included in the landmark analyses for very late ST. Multivariable analyses of predictors of ST were performed with Cox proportional hazards regression models. Clinical and angiographic variables with p values <0.1 on univariable analyses (Table 1) were entered into the Cox regression models. In addition, diabetes and stent type were entered into the models because of their clinical relevance. Backward elimination at alpha = 0.05 was used to select significant predictors. All analyses were performed with SPSS (version 19.0, IBM Incorporated, Armonk, New York) and SAS (version 9.2, SAS Institute, Cary, North Carolina) software.

Results

From 1995 through 2009, 1,640 consecutive patients undergoing primary PCI for STEMI were treated with BMS (n = 1,147) or DES (n = 410) or had STEMI due to ST and underwent PCI but did not receive a new stent (n = 83). Patients were followed prospectively for 1 to 15 years. Clinical follow-up was complete or out to at least 4 years in 85% of patients, with a median follow-up time of 3.7 years. Stent thrombosis occurred in 124 patients, including 42 patients with early ST (<30 days), 35 patients with late ST (31 days to 1 year), and 47 patients with very late ST (>1 year). The cumulative frequency of ST by Kaplan-Meier estimates was 2.7% at 30 days, 5.2% at 1 year, and 8.3% at 5 years (Fig. 1).

Of the 42 patients with early ST, 34 were definite, and 8 were probable, including 5 with sudden unexplained death within 30 days. Of the 82 patients with late or very late ST, 81 were definite, and 1 was probable ST. Compliance with dual antiplatelet therapy at the time of ST was present in 60% of patients with early ST, 52% of patients with late ST, and 12% of patients with very late ST.

Baseline clinical and angiographic variables and frequency of ST. Patients with ST have a higher frequency of prior myocardial infarction (MI) and STEMI due to ST (Table 1). The cumulative frequencies of ST out to 5 years by Kaplan-Meier

Table 1. Baseline Clinical and Angiographic Variables and Procedural Variables

				Kaplan-Meier Frequency of ST*				
				Variable Present		Variable Absent		
	ST (n = 124)	No ST (n = 1,516)	p Value	1 Yr	5 Yrs	1 Yr	5 Yrs	Log-Rank p Value
Clinical variables								
All patients				5.2%	8.3%			
Age ≥70 yrs	22 (17.7%)	355 (23.4%)	0.15	5.3%	7.6%	5.2%	8.7%	0.41
Women	29 (23.4%)	463 (30.5%)	0.095	4.1%	6.9%	5.7%	9.2%	0.10
Diabetes	19 (15.3%)	241 (15.9%)	0.87	7.3%	9.4%	4.9%	8.3%	0.76
Insulin-dependent diabetes	5 (4.0%)	59 (3.9%)	0.94	9.7%	9.6%	5.1%	8.4%	0.70
Current smoker	54 (43.5%)	746 (49.2%)	0.23	5.1%	8.7%	5.3%	8.2%	0.44
Prior infarction	32 (25.8%)	236 (15.6)	0.003	11.1%	14.9%	4.1%	7.3%	0.001
Prior bypass surgery	9 (7.3%)	78 (5.1%)	0.31	8.8%	9.0%	5.0%	8.5%	0.36
Anterior infarction	36 (29.0%)	560 (36.9%)	0.078	4.7%	6.9%	5.5%	9.3%	0.18
Killip class III–IV	16 (12.9%)	173 (11.4%)	0.62	11.5%	10.5%	4.6%	8.1%	0.041
Angiographic and procedural variables								
3-vessel coronary disease	30 (24.2%)	348 (23.0%)	0.75	6.4%	9.0%	4.9%	8.3%	0.64
LVEF <40%	24 (20.3%)	297 (20.7%)	0.92	7.3%	8.7%	4.6%	8.3%	0.50
Infarct vessel = vein graft	5 (4.0%)	37 (2.4%)	0.43	10.7%	10.9%	5.1%	8.4%	0.26
TIMI flow grade 0–1 pre-PCI	92 (74.2%)	1,149 (75.8%)	0.69	5.0%	8.8%	5.7%	8.4%	0.78
TIMI flow grade 0–2 post-PCI	3 (2.4%)	74 (4.9%)	0.21	3.7%	10.2%	5.3%	8.5%	0.59
Small stent size (<3.0 mm)	33 (26.6%)	314 (20.8%)	0.13	8.9%	10.6%	4.3%	7.9%	0.010
Multiple stents	28 (28.6%)	342 (28.3%)	0.95	6.7%	9.0%	5.0%	9.6%	0.91
Drug-eluting stent*	29 (25.2%)	381 (26.4%)	0.78	4.2%	12.8%	5.2%	7.4%	0.26
GPI used	93 (75.0%)	1,030 (67.9%)	0.104	6.0%	9.5%	3.5%	6.2%	0.039
STEMI due to ST	22 (17.7%)	145 (9.6%)	0.004	13.6%	16.9%	4.4%	7.6%	<0.001
Reperfusion time ≤2 h	15 (12.1%)	123 (8.1%)	0.12	10.2%	11.8%	4.8%	8.2%	0.080

Values are n (%). Comparison of event rates in patients with and without the index variable are made with log-rank tests. *Values listed represent Kaplan-Meier estimates of the cumulative frequency of stent thrombosis (ST) at 1 and 5 years.

GPI = glycoprotein IIb/IIIa platelet inhibitor; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

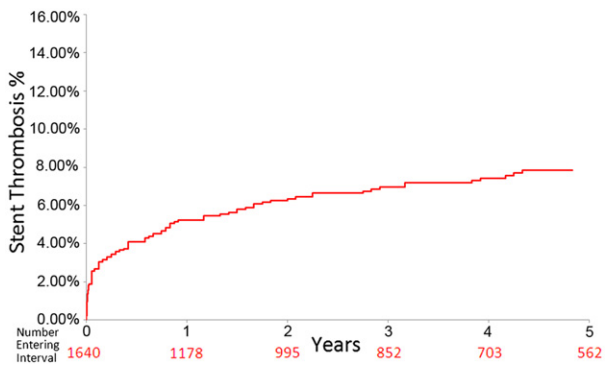

Figure 1. Cumulative Frequency of ST After Primary Percutaneous Coronary Intervention With Stenting in All Patients

The curve shows Kaplan-Meier estimates of definite or probable stent thrombosis (ST) (Academic Research Consortium criteria) out to 5 years.

analyses were significantly greater in patients with prior MI, Killip class III to IV, small stent size (<3.0 mm), glycoprotein IIb/IIIa inhibitor use, and STEMI due to ST (Table 1).

Patients with Killip class III to IV comprised 11.5% of our study population, and patients with STEMI due to ST comprised 10.2% of our study population.

Univariable correlates of early, late, and early or late ST and very late ST. Prior MI, Killip class III to IV, 3-vessel coronary disease, small stent size (<3.0 mm), and STEMI due to ST were significant univariable correlates of increased incidence of early ST (≤30 days) by Kaplan-Meier analyses (Table 2).

Prior MI, Killip class III to IV, STEMI due to ST, and reperfusion time (RT) ≤2 h were significant univariable correlates of increased frequency of late ST (landmark analyses 31 days to 1 year) (Table 2).

Prior MI, Killip class III to IV, small stent size (<3.0 mm), use of glycoprotein IIb/IIIa inhibitors, STEMI due to ST, and RT <2 h were significant univariable correlates of early or late ST (ST from Day 0 through 1 year) (Figs. 2A to 2E, Table 2).

The only significant univariable correlate of very late ST (landmark analyses >1 year) was the use of a DES compared with a BMS (7.0% vs. 1.7% from 1 to 5 years, $p < 0.001$) (Fig. 3). Because comparison of outcomes from different time periods could introduce bias when comparing DES with BMS (BMS were implanted from 1995 to 2009, whereas DES were implanted from 2003 to 2009), we analyzed the period 2003 to 2009 when both types of stents were being implanted. During this period there was a trend for an increased incidence of very late ST with DES (7.0% vs. 2.9% from 1 to 5 years, $p = 0.066$).

Multivariable predictors of early, late, early or late, and very late ST. ST-segment elevation myocardial infarction due to ST, Killip class III to IV, and small stent size (<3.0 mm) were significant multivariable predictors of early ST (0 to 30 days) by Cox regression (Table 3). Reperfusion time ≤2 h, prior MI, and diabetes were significant multivariable predictors of late ST (31 to 365 days). ST-segment elevation myocardial infarction due to ST, small stent size (<3.0 mm), Killip class III to IV, and RT ≤2 h were significant multivariable predictors of early or late ST (0 to 365 days). The use of a DES compared with a BMS was the only significant independent predictor of very late ST when all years were analyzed. When we analyzed only the years when both BMS and DES were implanted (2003 to 2009), there was a trend for higher rates of very late ST with DES (HR: 2.36, 95% CI: 0.92 to 6.03, $p = 0.073$).

Discussion

The major findings of this study are: 1) the frequency of ST after DES and BMS for STEMI is relatively high and continues to increase out to 5 years; and 2) the major predictors of early or late ST (0 to 1 year) are STEMI due to ST, small stent size (<3.0 mm), Killip class III to IV, and RT <2 h; the only predictor of very late ST (>1 year) is the use of DES versus BMS.

A number of studies have shown that the frequency of ST after stent implantation for STEMI is relatively high and that implantation of stents for STEMI is one of the strongest independent predictors of subsequent ST (3–8). In addition, there are several studies that have shown that the cumulative frequency of ST continues to increase out to 3 to 5 years and beyond (7,8,14). The frequency of ST in our study is higher than the frequency in the HORIZONS-AMI study and other studies, and this might be related to the inclusion of relatively large numbers of patients at high risk for ST, including patients with Killip class III to IV and patients with STEMI due to ST. Also, our study population is from an all-inclusive clinical setting rather than a randomized controlled trial, and as a consequence, our population might have poorer compliance with dual antiplatelet therapy and other therapies. Follow-up is longer in our study than previous studies and documents that the cumulative frequency of ST continues to increase out to at least 5 years.

Several studies have evaluated predictors of ST after stenting for STEMI. Smit et al. (17) evaluated 1,548 STEMI patients treated with stenting and found that Killip class >I was the only significant predictor of ST at 1 year. Ergelen et al. (18) evaluated 1,960 STEMI patients treated with stenting and found that stent diameter <3 mm, current smoker, and diabetes were the only significant independent predictors of 30-day ST. Dangas et al. (19) evaluated predictors of ST out to 2 years in 3,203 STEMI patients from the HORIZONS-AMI trial. Significant independent predictors of early ST (<30 days) were insulin-dependent diabetes, baseline Thrombolysis In Myocardial Infarction flow grade 0 to 1, higher baseline platelet count,

Table 2. Univariable Correlates of Frequency of Early, Late, and Early or Late ST*

	Frequency								
	Early ST			Late ST			Early or Late ST		
	Variable Present	Variable Absent	p Value	Variable Present	Variable Absent	p Value	Variable Present	Variable Absent	Log-Rank p Value
Clinical variables									
Age ≥70 years	2.9%	2.6%	0.81	2.5%	2.6%	0.86	5.3%	5.2%	0.95
Women	2.6%	2.7%	0.86	1.5%	3.1%	0.10	4.1%	5.7%	0.22
Diabetes	2.9%	2.7%	0.86	4.5%	2.3%	0.071	7.3%	4.9%	0.18
Insulin-dependent diabetes	5.4%	2.6%	0.24	4.5%	2.5%	0.42	9.7%	5.1%	0.15
Current smoker	2.2%	3.2%	0.25	2.9%	2.2%	0.40	5.1%	5.3%	0.78
Prior infarction	5.2%	2.2%	0.008	6.2%	1.9%	<0.001	11.1%	4.1%	<0.001
Prior bypass surgery	4.8%	2.6%	0.22	4.3%	2.5%	0.34	8.8%	5.0%	0.12
Anterior infarction	2.9%	2.6%	0.81	1.9%	3.0%	0.23	4.7%	5.5%	0.54
Killip class III–IV	6.8%	2.3%	<0.001	5.1%	2.4%	0.035	11.5%	4.6%	<0.001
Angiographic and procedural variables									
3-vessel coronary disease	4.2%	2.2%	0.047	2.3%	2.7%	0.78	6.4%	4.9%	0.20
LVEF <40%	3.8%	2.4%	0.21	3.7%	2.3%	0.21	7.3%	4.6%	0.074
Infarct vessel = vein graft	4.9%	2.6%	0.330	6.1%	2.5%	0.20	10.7%	5.1%	0.11
TIMI flow grade 0–1 pre-PCI	2.8%	2.3%	0.62	2.3%	3.5%	0.23	5.0%	5.7%	0.66
TIMI flow grade 0–2 post-PCI	0.0%	2.8%	0.17	3.7%	2.6%	0.47	3.7%	5.3%	0.56
Small stent size (<3.0 mm)	5.4%	2.0%	0.001	3.7%	2.3%	0.16	8.9%	4.3%	0.001
Multiple stents	3.7%	2.5%	0.21	3.1%	2.6%	0.72	6.7%	5.0%	0.24
Drug-eluting stent	1.8%	2.9%	0.21	2.5%	2.3%	0.90	4.2%	5.2%	0.35
GPI used	3.1%	1.8%	0.15	3.0%	1.7%	0.15	6.0%	3.5%	0.042
STEMI due to ST	7.8%	2.1%	<0.001	6.3%	2.3%	0.016	13.6%	4.4%	<0.001
Reperfusion time ≤2 h	3.8%	2.6%	0.40	6.7%	2.3%	0.009	10.2%	4.8%	0.018

Values listed represent Kaplan-Meier estimates of the cumulative frequency of early ST (30 days), late ST (31 to 365 days), and early or late ST (365 days). The p values refer to comparisons of Kaplan Meier estimates of the cumulative frequency of ST in patients with and without the index variable with the log-rank test.
Abbreviations as in Table 1.

no pre-randomization heparin, and low (300 vs. 600 mg) clopidogrel loading dose. Predictors of late ST (30 days to 1 year) were insulin-dependent diabetes, prior MI, and current smoking. Predictors of very late ST (1 to 2 years) were insulin-dependent diabetes, history of prior PCI, higher baseline platelet count, and use of heparin and glycoprotein IIb/IIIa inhibitor versus bivalirudin. Similar to these studies, our study found that Killip class III to IV, small stent size <3.0 mm, and prior MI were significant predictors of ST. Diabetes was an independent predictor of late ST, and there were trends for more early or late ST in patients with insulin-dependent diabetes. We also found that early RT was a significant predictor of early or late ST. The reasons for this are not clear. Early reperfusion was not a significant predictor of ST in the HORIZONS-AMI trial (19). It is possible that patients with early reperfusion have more viable myocardium and are more likely to present with an acute coronary syndrome and ST, rather than silent occlusion.

The use of a DES versus a BMS was the only significant predictor of very late ST in our study. Of the previous studies discussed in the preceding text, only the HORIZONS-AMI study evaluated predictors of very late ST, and the type of stent used (paclitaxel-eluting stent [PES] vs. BMS) was not a significant predictor (19). However, later follow-up out to 3 years in the HORIZONS-AMI study did show trends for increased rates of very late ST from 1 to 3 years with PES (PES 1.7% vs. BMS 0.9%, p = 0.12) (8). Other studies have shown conflicting results. Violini et al. (20) reporting from the SESAMI (Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction) trial and Spaulding et al. (14) reporting from TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty) found no difference in very late ST from 1 to 5 years between sirolimus-eluting stent and BMS. However, Vink et al. (15) found a higher frequency of very late ST with PES compared with BMS from 1 to 5 years in the PASSION (Paclitaxel Eluting Stent Versus Conventional Stent in ST-segment Elevation Myocardial Infarction) trial, and Brodie et al. (16) have previously reported a higher frequency of very late ST in patients with DES versus BMS in their large primary PCI registry. There has been concern about very late ST when DES are implanted in patients with STEMI, because of studies

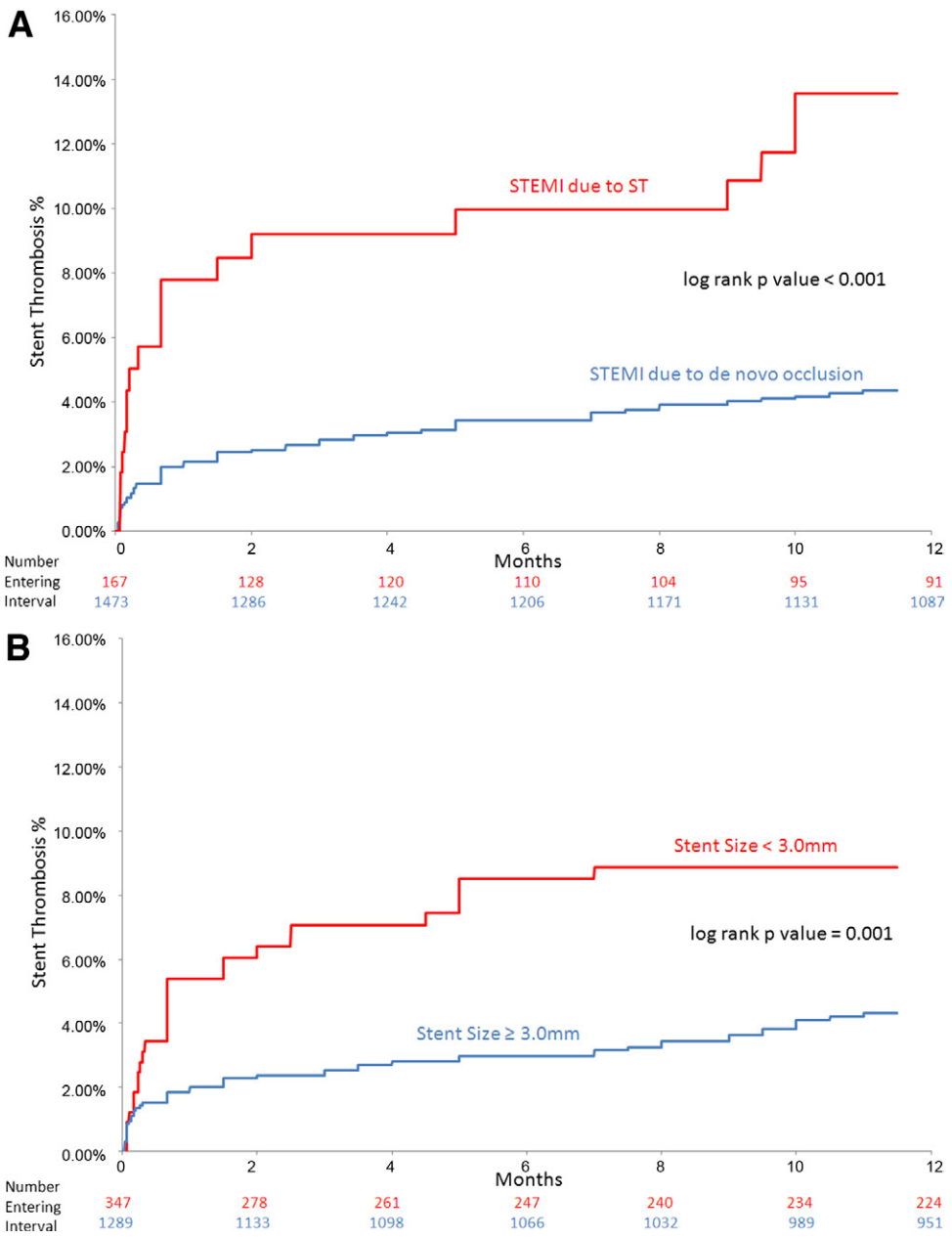

Figure 2. Selected Univariable Correlates of Early or Late Stent Thrombosis (0 to 365 Days)

Kaplan-Meier estimates of cumulative frequency of early or late stent thrombosis (ST) (0 to 1 year) (Academic Research Consortium definite or probable) after primary percutaneous coronary intervention with stenting for ST-segment elevation myocardial infarction (STEMI) in selected subgroups. **(A)** Compares patients with versus without STEMI due to stent thrombosis; **(B)** compares patients with stent size <3.0 versus ≥3.0 mm.

Continued on the next page.

showing an increased incidence of late stent malapposition and poor healing with DES compared with BMS (10–12). Our data and some of the data cited in the preceding text support that concern.

Study limitations. Our study has several important limitations. Our study spans 15 years during which time treatment strategies with primary PCI and stenting have shown considerable evolution. Different adjunctive treatments over this time period could affect our outcomes and affect the incidence and predictors of ST. Importantly, most of the stents used in this study were first- or second-generation BMS and first-generation DES, and our results might not be directly appli-

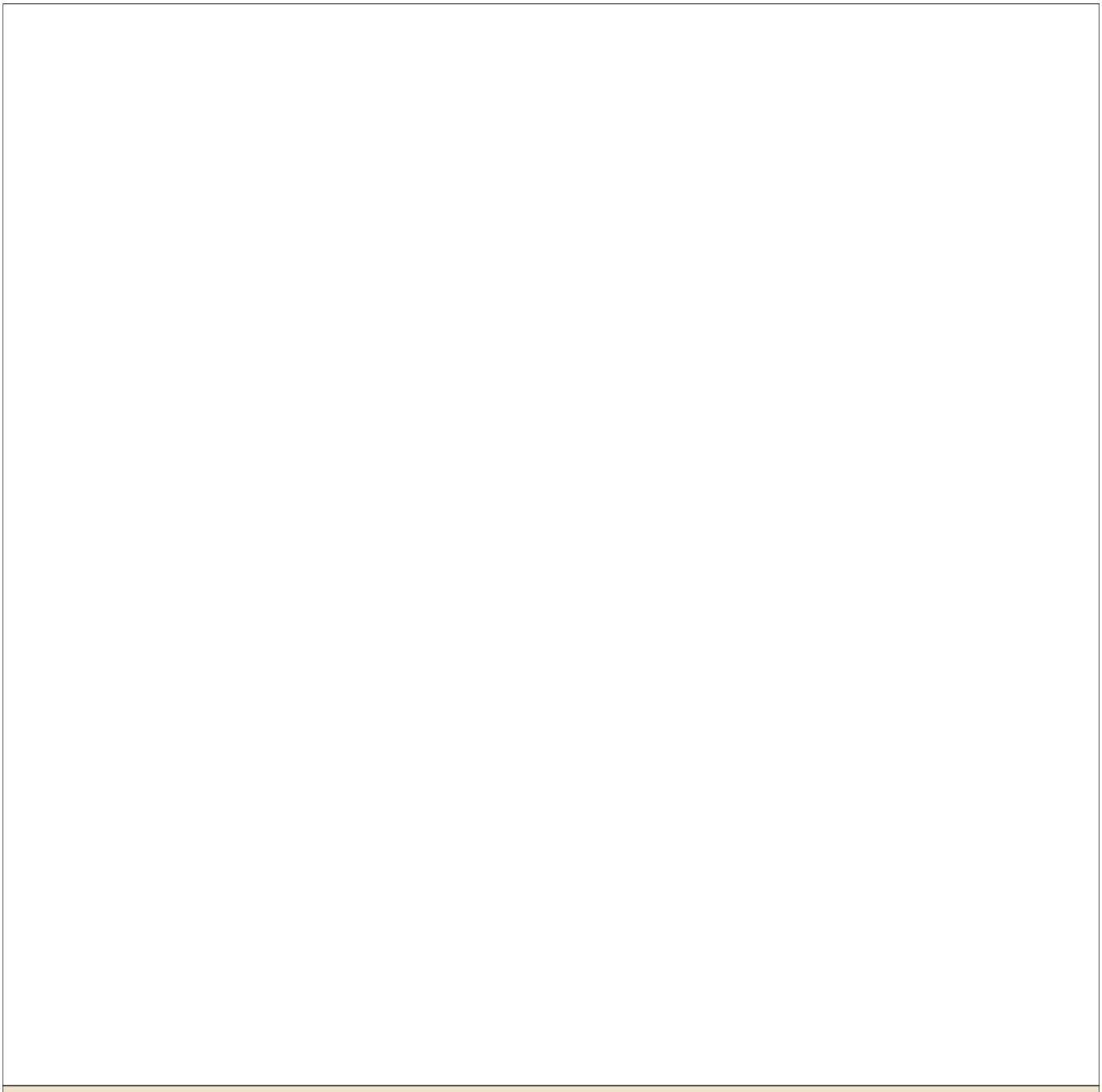

Figure 2. Continued

(C) compares patients with Killip class III to IV versus Killip class I to II; **(D)** compares patients with reperfusion time (RT) ≤2 h versus RT >2 h.

Continued on the next page.

cable to current-generation stents. Our data also precede the use of new antiplatelet agents, ticagrelor and prasugrel. We do not have complete data on compliance with dual antiplatelet therapy, which is an important determinant of ST. Only BMS were implanted from 1995 to 2002, whereas both BMS and DES were implanted from 2003 to 2009. Comparison of ST rates for BMS and DES during these different time periods could introduce bias. Follow-up was obtained with the help of electronic medical records, which could potentially introduce bias by obtaining follow-up in patients who are hospitalized with ST and missing follow-up in patients without ST, artificially increasing the frequency of ST.

Clinical implications. The relatively high incidence of ST after stenting for STEMI emphasizes the importance of developing new strategies for preventing this complication, including better deployment techniques, newer-generation

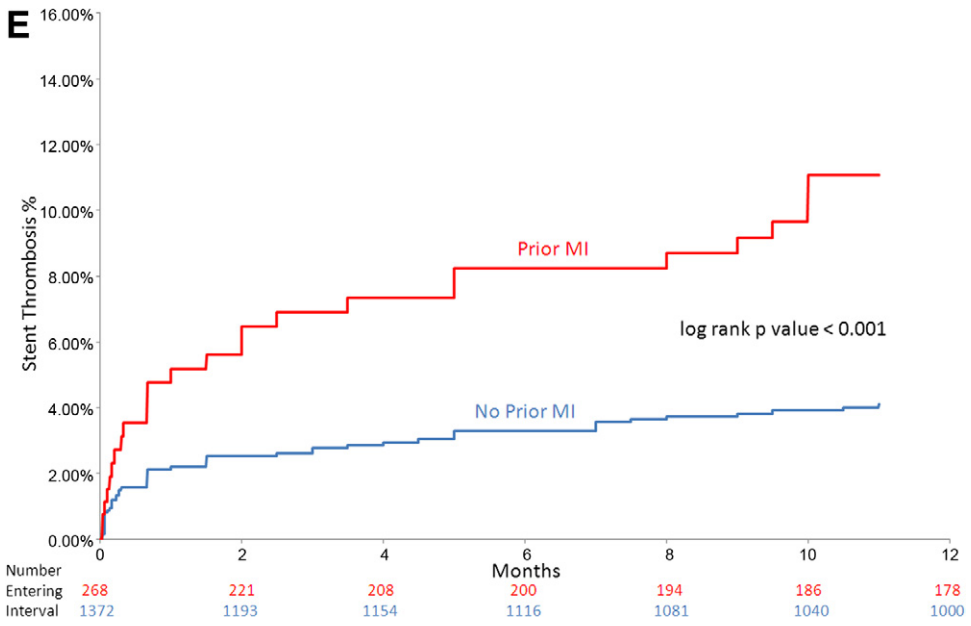

Figure 2. Continued

(E) compares patients with versus without prior myocardial infarction (MI).

DES, bioabsorbable polymers, bioabsorbable stent platforms, and better anticoagulant and antiplatelet therapies. Prasugrel and ticagrelor have been shown to dramatically reduce the frequency of ST in STEMI patients treated with stents and should be used in eligible patients (21–22). Alternative strategies include high-dose clopidogrel and measurement of platelet inhibition to guide therapy in patients not eligible for prasugrel or ticagrelor.

Patients at highest risk might be targeted for more aggressive therapies. For example, patients with STEMI due to ST might be considered for thrombectomy, intravascular ultrasound–guided PCI, and avoidance of a new

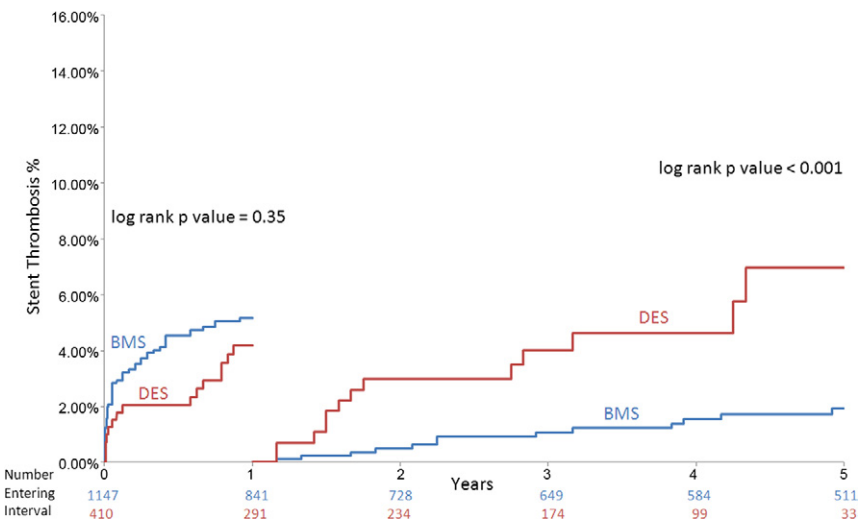

Figure 3. Landmark Analysis of ST Rates With DES Versus BMS for STEMI

The curves show Kaplan-Meier estimates of definite or probable stent thrombosis (ST) rates (Academic Research Consortium criteria) at 0 to 1 and >1 year. BMS = bare-metal stent(s); DES = drug-eluting stent(s); STEMI = ST-segment elevation myocardial infarction.

Table 3. Multivariable Predictors of Early, Late, Early or Late, and Very Late ST

	HR	95% CI	p Value
Early ST (0–30 days)			
STEMI due to ST	6.46	3.04–13.7	<0.001
Killip class III–IV	2.60	1.23–5.49	0.012
Small stent size (<3.0 mm)	2.58	1.35–4.95	0.004
Late ST (31 days−1 year)			
Reperfusion time <2 h	2.64	1.01–6.90	0.048
Prior infarction	2.57	1.17–5.63	0.019
Diabetes	2.29	1.05–5.03	0.038
Early or late ST (0–1 year)			
STEMI due to ST	4.38	2.27–8.45	<0.001
Small stent size (<3.0 mm)	2.44	1.49–4.00	<0.001
Killip class III–IV	2.39	1.30–4.40	0.005
Reperfusion time ≤2 h	2.09	1.03–4.24	0.040
Very late ST (>1 year)			
Drug-eluting stent	3.77	1.81–7.88	<0.001

CI = confidence interval; HR = hazard ratio; ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction.

stent in selected cases. If very late ST rates are truly higher with DES compared with BMS, the benefit of reduced restenosis with DES might not be worth the increased risk of very late ST, and BMS might be a more appropriate choice in many patients with STEMI. Prolonged dual antiplatelet therapy after the first year should also be considered in patients with first-generation DES.

Reprint requests and correspondence: Dr. Bruce R. Brodie, Moses H. Cone Memorial Hospital, The LeBauer Cardiovascular Research Foundation, 313 Meadowbrook Terrace, Greensboro, North Carolina 27408. E-mail: bbrodie89@gmail.com.

REFERENCES

1. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. N Engl J Med 1999;341:1949–56.
2. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 2002;346:957–66.
3. Urban P, Gershlick AH, Guagliumi G, et al. Safety of coronary sirolimus-eluting stents in daily clinical practice. One-year follow-up of the e-cypher registry. Circulation 2006;113:1434–41.
4. 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.
5. de la Torre-Hernández JM, Alfonso F, Hernández F, et al. Drug-eluting stent thrombosis. Results from the multicenter Spanish registry ESTROFA. J Am Coll Cardiol 2008;51:986–90.
6. Lagerqvist B, Carlsson J, Frobert O, et al. Stent thrombosis in Sweden. A report from the Swedish coronary angiography and angioplasty registry. Circ Cardiovasc Interventions 2009;2:401–8.
7. Kukreja N, Onuma Y, Garcia-Garcia HM, et al. The risk of stent thrombosis in patients with acute coronary syndromes treated with bare-metal and drug-eluting stents. J Am Coll Cardiol Intv 2009;209:534–41.
8. Stone GW, Witzenbichler B, Guagliumi G, et al. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. Lancet 2011;377:2193–204.
9. Dangas GD, Claessen BE, Mehran R, et al. Clinical outcomes following stent thrombosis occurring in-hospital versus out-of-hospital: results from the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial. J Am Coll Cardiol 2012;59:1752–9.
10. van der Hoeven BL, Liem SS, Jukema JW, et al. Sirolimus-eluting stents versus bare-metal stents in patients with ST-segment elevation myocardial infarction: 9-month angiographic and intravascular ultrasound results and 12-month clinical outcome results from the MISSION! Intervention Study. J Am Coll Cardiol 2008;51:618–26.
11. Guo N, Maehara A, Mintz GS, et al. Incidence, mechanisms, predictors and clinical impact of acute and late stent malapposition after primary intervention in patients with acute myocardial infarction: an intravascular ultrasound substudy of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. Circulation 2010;122:1077–84.
12. 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.
13. 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.
14. Spaulding C, Teiger E, Commeau P, et al. Four-year follow-up of TYPHOON (Trial to assess the use of the CYPHer sirolimus-eluting coronary stent in acute myocardial infarction treated with ballOON angioplasty). J Am Coll Cardiol Intv 2011;4:14–23.
15. Vink MA, Dirksen MT, Suttorp MJ, et al. 5-Year follow-up after primary percutaneous coronary intervention with a paclitaxel-eluting stent versus a bare-metal stent in acute ST-segment elevation myocardial infarction. J Am Coll Cardiol Intv 2011;4:24–9.
16. Brodie B, Pokharel Y, Fleishman N, et al. Very late stent thrombosis after primary percutaneous coronary intervention with bare-metal and drug-eluting stents for ST-segment elevation myocardial infarction. J Am Coll Cardiol Intv 2011;4:30–8.
17. Smit JJ, van't Hof AW, de Boer MJ, et al. Incidence and predictors of subacute thrombosis in patients undergoing primary angioplasty for an acute myocardial infarction. Thromb Haemost 2006;96:190–5.
18. Ergelen M, Uyarel H, Osmonov, et al. Early stent thrombosis in patients undergoing primary coronary stenting for acute myocardial infarction: incidence, a simple risk score, and prognosis. Clin Appl Thromb/Hemost 2010;16:33–41.
19. Dangas GD, Caixeta A, Mehran R, et al. Frequency and predictors of stent thrombosis after percutaneous coronary intervention in acute myocardial infarction. Circulation 2011;123:1745–56.
20. Violini R, Musto C, De Felice F, et al. Maintenance of long-term clinical benefit with sirolimus-eluting stents in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2010;55:810–4.
21. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomized controlled trial. Lancet 2009;373:723–31.
22. Steg PG, James S, Harrington RA, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a Platelet Inhibition and Patient Outcomes (Plato) trial subgroup analysis. Circulation 2010;122:2131–41.

Key Words: predictors stent thrombosis ■ primary PCI ■ STEMI ■ stent thrombosis.