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Angiographic Stent Thrombosis at Coronary Bifurcations

Short- and Long-Term Prognosis

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Objectives This study sought to describe the presentation, management, and outcomes of patients presenting with angiographic definite stent thrombosis (ST) at coronary bifurcations.

Background The development of drug-eluting stents has made it increasingly feasible to treat bifurcation lesions percutaneously. However, ST at coronary bifurcations may be associated with greater mortality than ST elsewhere.

Methods We analyzed a multicenter California registry comprising all cases of angiographic definite ST at 5 academic hospitals from 2005 to 2010. Stenting was defined as occurring at a bifurcation if the main vessel stent crossed a side branch ≥2.0 mm in diameter (provisional single-stent approach), or if there was a prior 2-stent bifurcation approach.

Results Among 173 cases of angiographic definite ST, we identified 20 cases of ST at coronary bifurcations. Nine of 20 bifurcation ST (45%) occurred with a stent present in both the parent and branch vessel. Eight cases had thrombus present in both the parent and side branch vessels. In-hospital mortality was much higher for subjects with bifurcation ST than ST at a nonbifurcation site (20% vs. 2%, $p < 0.0001$). During a median follow-up of 2.3 years, ST at a coronary bifurcation was associated with increased long-term mortality (hazard ratio [HR]: 3.3, 95% confidence interval [CI]: 1.4 to 7.7, $p = 0.007$) and a significantly higher risk for major adverse cardiovascular events (HR: 2.2, 95% CI: 1.04 to 4.8, $p = 0.04$) relative to ST at a nonbifurcation site.

Conclusions ST at coronary bifurcations is associated with a higher in-hospital and long-term mortality than ST at nonbifurcation lesions. (Stent Thrombus in Acute Coronary Syndromes; NCT00931502) (J Am Coll Cardiol Intv 2012;5:57–63) © 2012 by the American College of Cardiology Foundation

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Stent thrombosis (ST) is a rare complication of percutaneous coronary intervention (PCI) but is associated with high morbidity and mortality. Many factors may predispose the development of ST, including procedural variables, patient pre-disposition to thrombosis, and properties of the stent (1). Although ST was initially reported to have an in-hospital mortality exceeding 30%, recent studies have reported lower but still significant short-term mortalities ranging from 5% to 10% (2–8). Improved understanding of the risk factors for immediate and long-term adverse outcomes among subjects who develop ST might help with risk stratification and management of these challenging cases (4).

The percutaneous treatment of bifurcation lesions with bare-metal stents was limited due to the prohibitively high restenosis rates. The availability of drug-eluting stents (DES) with significantly lower restenosis rates has made it possible to percutaneously treat many bifurcation lesions that might otherwise require surgical bypass (9). However, PCI at a coronary bifurcation is associated with a small but increased risk of ST, ranging from 1% to 3% at mean follow-up of 10 months in randomized studies of bifurcation stenting (10). Bifurcation PCI may also be an independent risk factor for development of very late ST (11). Furthermore, ST at coronary bifurcations may jeopardize a greater territory of myocardium at risk and potentially increase the risk of adverse cardiovascular outcomes (12). Therefore, we hypothesized that patients with ST at coronary bifurcations would have higher mortality than patients who develop ST at nonbifurcation sites. To answer this question, we compared presentations and outcomes among patients in a multicenter California registry of patients who presented with angiographic definite ST, and we stratified our analysis based on the presence of ST at a coronary artery bifurcation.

Abbreviations and Acronyms

CABG = coronary artery bypass graft
CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
MACE = major adverse cardiac event(s)
PCI = percutaneous coronary intervention
ST = stent thrombosis
STEMI = ST-segment elevation myocardial infarction

Methods

The University of California ST registry contains all consecutive cases of angiographically determined definite ST at 5 academic medical centers (University of California, Davis; University of California, San Diego; San Francisco Veteran's Administration Hospital; San Francisco General Hospital; and University of California, San Francisco Moffitt-Long Hospital) from 2005 to 2010 (8). Cases were identified using cardiac catheterization laboratory records and, from 2008 onward, prospective enrollment of subjects. After identification of a potential ST, each case was reviewed for clinical and angiographic characteristics by 2 interventional cardiologists using the Academic Research Consortium criteria for definite ST (13). Only cases of angiographically determined definite ST were included in the registry.

Once identified, definite ST cases were reviewed for demographic, procedural, angiographic, and in-hospital outcomes, as described previously (8). Briefly, trained abstractors and physicians reviewed each medical chart for details of presentation, medication compliance, and in-hospital outcomes (death, stroke, or repeat myocardial infarction). Stent thrombosis was defined as occurring "early" if the event occurred ≤30 days after the index PCI; "late" if it occurred 1 month to 1 year after the index PCI; and "very late" if it occurred >1 year after index PCI. Long-term mortality was assessed using hospital records, patient follow-up, and the Social Security Death Index. Subjects were also prospectively enrolled in a follow-up phone interview to assess for the occurrence of repeat myocardial infarction, revascularization, or stroke.

An interventional cardiologist blinded to outcomes reviewed the procedural details of each case, including location of thrombus within the stent, whether thrombus was present in the main and/or side branch vessels, TIMI (Thrombolysis In Myocardial Infarction) flow grade, and thrombus grading. Thrombus grading was angiographically scored into 5 grades: 0 if there was no apparent thrombus; 1 if possible thrombus was seen; 2 if definite thrombus was <0.5 the vessel diameter; 3 if definite thrombus was 0.5 to 2 vessel diameters; 4 if definite thrombus was >2 vessel diameters; and 5 if there was complete vessel occlusion from thrombus (14). In cases where there was complete stent occlusion by thrombus, thrombus grading was also recorded after initial lesion crossing with a wire but before balloon inflation. A stent was defined as occurring at a bifurcation if the main vessel stent crossed a side branch ≥2.0 mm in diameter (designated a provisional single-stent approach) or if there were 2 stents present, with 1 originating in a main vessel and the second in a side branch (designated a 2-stent bifurcation approach).

Institutional review board approval was obtained at each site. Informed consent was obtained for prospectively enrolled patients, whereas chart review was performed for retrospectively identified patients. Retrospectively identified patients were also contacted to provide informed consent for a telephone interview. The trial has been registered with identifier NCT00931502.

Statistical analyses. Median values with interquartile ranges were used to describe continuous variables, and numerical values (percentages) were used for categorical variables. Univariate analysis was used to identify differences between subjects with ST at bifurcation versus nonbifurcation sites. Continuous variables were compared using the Kruskal-

Wallis test. Categorical values were compared by the chi-square or Fisher exact test. Because most bifurcation ST occurred at left anterior descending artery/diagonal branch locations, a sensitivity analysis limited to ST of these vessels was also performed. Long-term mortality was analyzed using Kaplan-Meier survival analysis and log-rank test. A Cox proportional hazards model was developed to explore the relationship between bifurcation ST and risk of mortality and major adverse cardiac events (MACE). Known risk factors for mortality (age, presentation with ST-segment elevation myocardial infarction [STEMI], diabetes, chronic kidney disease) were automatically included. Then, a list of possible confounders was generated using a directed acyclic graph. Confounders from this second group were retained if they were found to be associated with the outcome, using a p value <0.1 as a cutoff for inclusion. The final variables in the model included age, sex, diabetes, history of chronic kidney disease, prior coronary artery bypass graft (CABG), type of thrombosed stent (DES or bare-metal stent), and the involved vessel. The proportional hazards assumption was verified using log-log plots. All analyses were performed using Stata (version 11.0, STATA Corporation, College Station, Texas). A p value <0.05 was considered significant. All authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Among 173 cases of angiographically determined definite ST, we identified 20 cases of angiographically determined definite ST at coronary bifurcations, representing 12% of cases in the registry. Compared with subjects with ST at nonbifurcation locations (n = 153), subjects with bifurcation ST were younger (median: 57 vs. 61 years, p = 0.03) and were less likely to have previous CABG (0% vs. 15%, p = 0.07) or to be taking aspirin (58% vs. 78%, p = 0.05) or a thienopyridine (26% vs. 48%, p = 0.08) at presentation (Table 1). There was no difference in timing of ST between groups, with most ST presenting very late regardless of bifurcation status. Subjects with ST at a coronary bifurcation were, however, more likely to have ST of a DES (80% vs. 48%, p = 0.02). There was a trend toward a higher risk clinical presentation among subjects with ST of a coronary bifurcation, with a higher percentage of patients presenting with STEMI (80% vs. 64%) and with cardiogenic shock (25% vs. 20%).

The angiographic characteristics of patients with ST at a coronary bifurcation are summarized in Table 2. Nine of 20 cases (45%) occurred at bifurcations with a stent present in both the parent and branch vessel; the other 11 cases occurred at a bifurcation with a single stent overlapping a jailed side branch. Among subjects with thrombosis of 2 stents, the initial implantation technique was Culotte in 6 (67%), simultaneous kissing stents in 1, and unknown in 2. The pre-intervention TIMI flow grade was 0 in 70% of cases. Most cases (55%) involved left anterior descending artery/diagonal bifurcations, whereas the remainder consisted of ST at circumflex/obtuse marginal bifurcations and 1 case of a left main ST. The majority (85%) of patients had grade 4 or 5 thrombus within the stented region at the time of initial angiography and before balloon inflation. The thrombus originated in the proximal stented region in 16 (80%) cases. Eight of 20 (40%) cases had thrombus present in both the parent and side branch vessels. Single-stent and 2-stent ST had a similar prevalence of thrombus extension into the side branch (36% vs. 44%, p = NS), suggesting that the presence of a stent in the branch vessel was not associated with increased thrombus burden. Intravascular ultrasound was performed in 8 patients: this showed parent vessel stent underexpansion in 3 cases and stent malapposition in 2 cases. None of the cases had angiographic or intravascular ultrasound evidence of residual dissection or stent protrusion into the parent vessel.

Treatment of bifurcation ST included balloon angioplasty of the target vessels and new stent implantation in at least 1 vessel in 17 of 20 cases. Consistent with a more acute presentation, subjects with ST at a coronary bifurcation were more frequently treated with aspiration thrombectomy, heparin, glycoprotein IIb/IIIa antagonists, and intra-aortic balloon counterpulsation (Table 1). All patients were discharged on dual antiplatelet therapy.

In-hospital outcomes are summarized in Table 3. Procedural success, defined as $<30\%$ residual stenosis with TIMI flow grade 3 at the conclusion of the procedure, was 100% in cases of ST at coronary bifurcations, as compared to 88% in cases of ST at nonbifurcations (p = 0.1). Despite high procedural success, the peak creatine kinase and creatine kinase-myocardial band levels were higher for subjects with ST at bifurcation (median peak creatine kinase: 2,487 vs. 787 mg/dl, p = 0.02), which is consistent with a large area of myocardium at risk from the ST event. The rates of referral for CABG were similar (5% vs. 6%, p = 0.7). In-hospital mortality was significantly increased for subjects with bifurcation ST (20% vs. 2%, p < 0.0001). All in-hospital deaths were due to heart failure. In-hospital mortality remained significantly higher when the analysis was limited only to ST of the left anterior descending artery/diagonal territory (20% vs. 3%, p = 0.03). Case mortality was 33% for 2-stent bifurcations and 9% for single-stent bifurcations (p = 0.4). Two of the in-hospital deaths were from very late ST.

The Kaplan-Meier survival estimates for mortality and major adverse cardiovascular events are shown in Figures 1 and 2. During a median follow-up of 2.3 years, ST at a coronary bifurcation was associated with increased long-term mortality (hazard ratio [HR]: 3.3, 95% confidence interval [CI]: 1.4 to 7.7, p = 0.007). Bifurcation ST was

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Table 1. Characteristics of Subjects With Angiographic Definite ST at Coronary Bifurcations

	ST at Bifurcation (n = 20)	ST at Nonbifurcation (n = 153)	p Value
Demographic characteristics			
Age, yrs	57 (45–62)	61 (52–71)	0.03
Male	16 (80)	133 (87)	0.40
Prior CABG	0 (0)	22 (15)	0.07
Diabetes	7 (37)	59 (39)	0.80
Hypertension	16 (80)	118 (77)	0.80
Prior MI	14 (74)	105 (69)	0.70
Chronic kidney disease	1 (5)	22 (14)	0.20
Ejection fraction	45 (40–55)	50 (25–60)	0.30
Indication for initial stent implantation			0.30
Acute coronary syndrome	15 (75)	96 (63)	
Stable angina	5 (25)	57 (37)	
Timing of ST			0.60
Early	4 (20)	43 (30)	
Late	4 (20)	22 (16)	
Very late	12 (60)	76 (54)	
Taking aspirin	11 (58)	114 (78)	0.05
Taking thienopyridine	5 (26)	70 (48)	0.08
Presentation			0.50
STEMI	16 (80)	97 (64)	
NSTEMI	4 (20)	33 (22)	
Unstable angina	0 (0)	16 (11)	
Primary PCI	16 (80)	102 (67)	0.20
Cardiogenic shock	5 (25)	30 (20)	0.60
Type of thrombosed stent(s)			0.02
DES	16 (80)	72 (48)	
BMS	1 (5)	40 (27)	
Unknown	3 (15)	39 (26)	
Angiographic details			
Target vessel			0.02
LAD	12 (60)	70 (46)	
RCA	0	46 (30)	
Circumflex	7 (35)	25 (16)	
Bypass graft	0	11 (7)	
Target vessel location			0.20
Proximal	14 (70)	80 (54)	
Mid-distal	6 (30)	68 (46)	
TIMI flow grade <3	16 (80)	140 (92)	0.10
Reference vessel diameter, mm	3.0 (2.5–3.2)	3.0 (2.6–3.5)	0.80
Procedural treatment			
Thrombectomy	14 (70)	79 (52)	0.10
Balloon angioplasty alone	3 (15)	49 (33)	0.10
GP IIb/IIIa antagonist	18 (100)	114 (80)	0.04
Antithrombotic			0.05
Heparin	19 (95)	114 (76)	
Bivalirudin	1 (5)	30 (20)	
IABP	5 (25)	20 (14)	0.20

Values are median (interquartile range) or n (%).

BMS = bare-metal stent(s); CABG = coronary artery bypass graft; DES = drug-eluting stent(s); GP = glycoprotein; IABP = intra-aortic balloon pump; LAD = left anterior descending artery; MI = myocardial infarction; NSTEMI = non– ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

Table 2. Angiographic Findings Among Subjects With ST at Coronary Bifurcations

Subject #	Timing of ST	Bifurcation Technique for Initial Stent Implantation	Parent Vessel	Side Branch Vessel	Pre-Intervention TIMI Flow Grade	Thrombus Grade	Location of Thrombus in Stent	Thrombus in Both Vessels	Treatment of ST
1	Early	Culotte	LAD	Diagonal	0	5 (4)	Proximal	Yes	Kissing balloon angioplasty
2	Early	Culotte	Circumflex	OM	0	3	Mid	No	BMS to circumflex
3	Early	Provisional	Circumflex	OM	0	5 (4)	Proximal	No	DES to LAD and diagonal
4	Early	Culotte	LAD	Diagonal	0	5 (4)	Proximal	Yes	Kissing balloon angioplasty
5	Late	SKS	LAD/left main	Circumflex	3	3	Mid	No	Kissing balloon angioplasty
6	Late	Provisional	LAD	Diagonal	1	4	Proximal	No	2 DES to LAD; kissing POBA to diagonal
7	Late	Culotte	LAD	Diagonal	0	5 (4)	Proximal	No	DES to LAD
8	Late	Unknown—2 stents	Circumflex	OM	0	5 (4)	Proximal	No	DES to circumflex and OM
9	Late	Provisional	LAD	Diagonal	0	5 (3)	Proximal	Yes	DES to LAD
10	Late	Provisional	Circumflex	OM	0	4	Proximal	Yes	DES to circumflex and OM
11	Very late	Unknown—2 stents	LAD	Diagonal	2	4	Proximal	Yes	DES to LAD and diagonal
12	Very late	Culotte	LAD	Diagonal	3	1	Mid	No	DES to LAD; POBA to diagonal
13	Very late	Provisional	LAD	Diagonal	0	4	Proximal	No	DES to LAD and diagonal
14	Very late	Provisional	Circumflex	OM	0	5 (4)	Proximal	Yes	DES to circumflex; POBA to OM
15	Very late	Provisional	OM	Circumflex	0	4	Proximal	No	DES to OM
16	Very late	Provisional	LAD	Diagonal	3	4	Proximal	No	BMS to LAD
17	Very late	Provisional	Circumflex	OM	3	5 (4)	Proximal	Yes	DES to circumflex and OM
18	Very late	Provisional	LAD	Diagonal	0	5 (3)	Distal	No	2 BMS to LAD
19	Very late	Provisional	Diagonal	LAD	0	5 (4)	Proximal	No	DES to diagonal; POBA to LAD
20	Very late	Culotte	LAD	Diagonal	0	5 (4)	Proximal	Yes	DES to diagonal; POBA to LAD

Thrombus grade in parentheses represent TIMI thrombus grade after initial wire crossing in cases of complete stent occlusion from thrombus.
OM = obtuse marginal; POBA = balloon angioplasty only; SKS = simultaneous kissing stent; other abbreviations as in Table 1.

also associated with a higher risk for MACE (HR: 2.2, 95% CI: 1.04 to 4.8, p = 0.04) relative to ST at a nonbifurcation site. MACE among patients with bifurcation ST included recurrent ST in 2 patients, which occurred 18 and 159 days after the initial ST. Both patients subsequently died during readmission for recurrent ST. Other MACE included 1 patient who required repeat target lesion revascularization and another who was referred for CABG.

After multivariable adjustment, including the type of thrombosed stent and the involved vessel, bifurcation ST remained associated with an increased risk of death and MACE during long-term follow-up (adjusted HR for death: 6.7, 95% CI: 2.3 to 19.9, p = 0.001; adjusted HR for MACE: 3.7, 95% CI: 1.5 to 9.1, p = 0.005).

Table 3. In-Hospital Outcomes of Subjects With Coronary Bifurcation ST

Outcome	ST at Bifurcation (n = 20)	ST at Nonbifurcation (n = 153)	p Value
Procedural success	20 (100)	130 (88)	0.10
Peak CK	2,487 (778–4,664)	787 (285–2,472)	0.02
Peak CK-MB	220 (84–300)	69 (25–233)	0.03
Referral for CABG	1 (5)	9 (6)	0.70
In-hospital mortality	4 (20)	3 (2.0)	<0.0001

Values are n (%) or median (interquartile range).
CK = creatine kinase; CK-MB = creatine kinase-myocardial band; other abbreviations as in Tables 1 and 2.

Discussion

The major finding of this study is that angiographic ST at a coronary bifurcation is associated with much higher in-hospital and long-term mortality than angiographic ST at nonbifurcation locations. This high mortality occurred despite high rates of procedural and angiographic success,

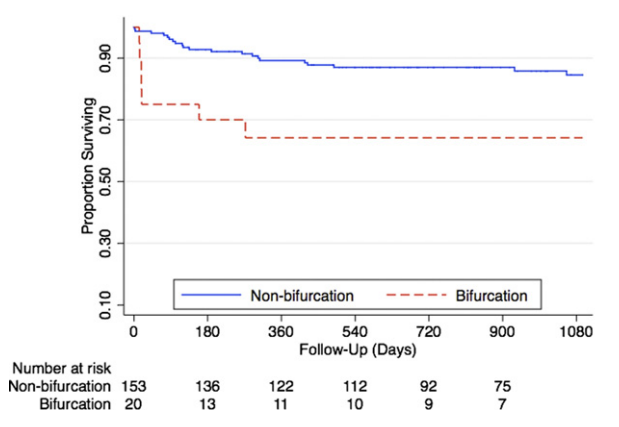

Figure 1. Long-Term Mortality of Subjects With Angiographic ST at Coronary Bifurcations

Stent thrombosis (ST) at a coronary artery bifurcation was associated with a statistically significant increased long-term mortality (p = 0.004 by log-rank test).

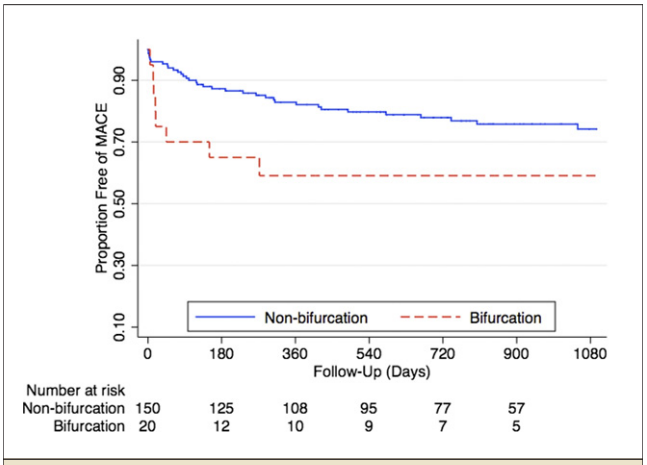

Figure 2. Long-Term MACE of Subjects With Angiographic ST at Coronary Bifurcations

Stent thrombosis (ST) at a coronary artery bifurcation was also associated with a greater long-term risk of major adverse cardiac events (MACE) ($p = 0.04$ by log-rank test).

emphasizing the importance of developing strategies to prevent ST before it occurs at a coronary bifurcation.

Previous studies have consistently shown that stenting at coronary bifurcations is associated with an increased risk of subsequent ST (6,15,16). In a recent meta-analysis of 1- versus 2-stent bifurcation techniques, the risk of ST was similar regardless of technique (10). Most studies have limited long-term follow-up; thus, the long-term risk of ST at previously treated bifurcation lesions is unknown. Because our cohort included only cases of angiographically determined definite ST, we cannot determine with certainty the relative incidence of ST at bifurcation versus nonbifurcation sites, as the Academic Research Consortium definition of ST includes sudden death and subsequent autopsy diagnosis. The mechanisms leading to an increased incidence of ST in bifurcation stenting is also uncertain, but it may be related to greater total stent length, impaired vessel healing, or flow disturbance at the bifurcation (17,18). In an autopsy series of bifurcation lesions, DES implantation was associated with a greater number of uncovered stent struts and fibrin deposition at the flow divider region versus at the lateral walls (19). This observation suggests that impaired vessel healing at the flow divider segment of a bifurcation may be a nidus for initiation of platelet aggregation and thrombus propagation.

Among studies that have examined outcomes after occurrence of an ST event, previously identified predictors of subsequent adverse outcomes have included total stent length, diabetes, depressed ejection fraction, and anatomically complex lesions (2,4). Bifurcation disease was not an independent predictor of adverse events in these studies. Our cohort differs in several characteristics, including a higher prevalence of very late ST, which may explain the difference in observed predictors of subsequent outcomes after ST. Also, bifurcation lesions are by definition anatomically complex and involve a longer total stent length than nonbifurcation lesions do. Clinically, however, identification of a bifurcation is more meaningful than measuring total stent length or classification of a lesion based on complexity.

Subjects with angiographic ST at coronary artery bifurcations had a high mortality despite angiographic and procedural success. The high mortality was primarily due to in-hospital death from heart failure, but also correlated with continued risk of death and MACE at a median follow-up of more than 2 years. This higher mortality is at least partly explained by a larger area of myocardium at risk among subjects with bifurcation ST, as the peak creatine kinase and creatine kinase-myocardial band were higher among these patients as compared to subjects with ST at nonbifurcation sites. This suggests that, despite procedural success, patients with bifurcation ST may be at higher risk of subsequent left ventricular dysfunction. Additionally, the high prevalence of thrombus in both the main and side branch vessel likely resulted in greater distal embolization and microvascular dysfunction. Consistent with this finding, higher thrombus burden is associated with higher subsequent MACE, both in de novo STEMI and after ST (20). Aspiration thrombectomy and glycoprotein IIb/IIIa inhibitors were used with increased frequency among patients with ST at coronary bifurcations, but not in all cases. It is possible that more liberal use of these adjunct agents to reduce thrombus burden could improve outcomes in ST at coronary bifurcations.

In the absence of other specific therapies, prevention of ST at coronary bifurcations remains paramount. Most patients with ST at coronary bifurcations were not taking a thienopyridine at the time of presentation. In fact, the rate of antiplatelet medication (aspirin and/or thienopyridine) usage was lower among subjects with ST at a bifurcation than among the overall cohort of subjects with ST. Although guidelines only require dual antiplatelet therapy for 1 year after stent implantation, the high mortality of bifurcation ST may be a relative indication for continuing dual antiplatelet therapy for more than 1 year in cases of bifurcation stenting. Because a high proportion of patients were not taking aspirin at presentation, it is possible that compliance after treatment of bifurcation ST was also low, thereby accounting at least in part for the higher rate of MACE. Additional strategies to reduce the occurrence of ST, such as administration of prasugrel in appropriate patients, could also be considered (21).

Study limitations. This study should be interpreted in the context of several limitations. First, the study population included only cases of angiographically determined definite ST. This may have resulted in selection bias, as patients that did not live to hospital admission or who did not undergo coronary angiography were not included in the cohort.

Second, this study cannot make any statement about the relative incidence of ST, as we identified patients at the time of ST, rather than at the time of initial stent implantation. Therefore, the increased prevalence of DES at bifurcations does not necessarily reflect an increased risk of ST from DES, but rather the preferential use of DES at bifurcation lesions to prevent restenosis. Likewise, the high prevalence of very late ST (50% in this study) reflects the population-attributable risk of very late ST (i.e., more subjects at risk who underwent PCI >1 year prior as compared to ≤1 year), rather than an increased incidence of very late ST.

Conclusions

Bifurcation ST is associated with significantly increased in-hospital mortality compared to ST at nonbifurcation sites despite aggressive intraprocedural anticoagulation and mechanical support. Continued efforts to prevent ST will be paramount to improving long-term outcomes of PCI at coronary bifurcations.

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