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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

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Objectives The study sought to determine whether rapid access to medical care and reperfusion results in a better prognosis in patients with in-hospital compared with out-of-hospital stent thrombosis (ST) in patients with ST-segment elevation myocardial infarction (STEMI) in the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial.

Background Whether the prognosis of in-hospital and out-of-hospital ST are similar is uncertain, with conflicting data reported from prior studies.

Methods A total of 3,602 STEMI patients undergoing primary percutaneous coronary intervention (PCI) were randomized to bivalirudin (n = 1,800) versus unfractionated heparin (UFH) plus a glycoprotein IIb/IIIa inhibitor (GPI) (UFH+GPI; n = 1,802). Stents were implanted in 3,202 patients, 156 (4.9%) of whom developed Academic Research Consortium definite/probable ST during 3-year follow-up. We investigated the 1-year clinical outcomes after ST in 54 patients with in-hospital ST compared with 102 patients with out-of-hospital ST.

Results One year after the ST event, patients with in-hospital compared with out-of-hospital ST had significantly greater mortality (27.8% vs. 10.8%, $p < 0.01$); most deaths in both groups occurred within 1 week of the ST event. Patients with in-hospital ST also had higher rates of major bleeding (21.2% vs. 6.0%, $p < 0.01$), but a lower rate of myocardial infarction (56.6% vs. 77.5%, $p < 0.01$). Subgroup analysis within both in-hospital and out-of-hospital ST groups indicated that subacute ST had the highest mortality. By multivariable analysis, 1-year mortality was significantly increased in patients with in-hospital compared with out-of-hospital ST (adjusted hazard ratio: 4.62, 95% confidence interval: 1.98 to 10.77, $p < 0.01$). Additional correlates of increased mortality after an ST event included diabetes and randomization to UFH+GPI (vs. bivalirudin).

Conclusions Following primary PCI for STEMI, more than one-third of all ST events during 3-year follow-up occurred during the index hospital phase. Mortality and major bleeding were significantly higher after in-hospital ST compared with out-of-hospital ST. (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; NCT00433966) (J Am Coll Cardiol 2012;59:1752–9) © 2012 by the American College of Cardiology Foundation

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Although uncommon, stent thrombosis (ST) after percutaneous coronary intervention (PCI) is associated with high rates of morbidity and mortality (1–4). Conceptually, the prognosis following ST may depend on how rapidly reperfusion is restored. One might presume that out-of-hospital ST would have a more dire prognosis than ST occurring in-hospital due to the absence of readily available resuscitation or coronary angiography/PCI capabilities. However, no systematic large series of ST has reported on the potential differences in outcomes when an ST event occurs during a hospitalization versus in an out-of-hospital setting.

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We have previously reported that ST occurred in approximately 4% of patients during the 2-year follow-up after primary PCI for ST-segment elevation myocardial infarction (STEMI) in patients enrolled in the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial (5,6). In the present analysis, we report the clinical outcomes after in-hospital versus out-of-hospital ST from the HORIZONS-AMI trial, including 3-year follow-up after the original index STEMI and study enrollment.

Methods

The HORIZONS-AMI trial has been described in detail previously (5,6). In brief, 3,602 patients admitted with STEMI presenting within 12 h after symptom onset undergoing a primary PCI management strategy were randomized (1:1) to receive either bivalirudin monotherapy (plus bailout glycoprotein IIb/IIIa inhibitor [GPI]) or unfractionated heparin (UFH) plus a GPI before PCI. Following angiography, stents were implanted in 3,202 patients, including 3,006 who were randomized (3:1) to TAXUS Express2 paclitaxel-eluting stents or otherwise identical bare metal stents (Boston Scientific, Natick, Massachusetts). Clinical follow-up was performed at 30 days, 6 months, 1 year, 2 years, and 3 years. The outcomes of patients in whom ST developed during the hospital period versus out-of-hospital were compared.

Abbreviations and Acronyms

GPI = glycoprotein IIb/IIIa inhibitor
PCI = percutaneous coronary intervention
ST = stent thrombosis
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction
UFH = unfractionated heparin

Stent thrombosis was defined according to the Academic Research Consortium ST definite or probable criteria (7), and all ST events were adjudicated by an independent clinical events committee blinded to pharmacology and stent assignment after review of original source documentation. The HORIZONS-AMI trial definitions for ischemic and bleeding events were used throughout this study, as previously reported (8).

Statistical analysis. Categorical variables were compared with Fisher's exact test, and continuous variables with Student's *t* test. Starting from the time of the first ST event per patient, time-to-event curves were derived using Kaplan-Meier methods. Landmark analyses were utilized to distinguish adverse events occurring in 3 distinct time periods after the occurrence of ST: 0 to 7 days, 7 to 30 days, and 30 days to 1 year. Time-to-event data were compared using log-rank tests and univariate Cox proportional hazards methods.

Logistic regression was used to identify the independent predictors of in-hospital and out-of-hospital ST. Two multivariable time-updated covariate-adjusted Cox proportional hazards models were used to investigate the relative impact of in- versus out-of-hospital ST on mortality. To prevent over-fitting, the first model utilized a limited number of covariates, and the second model used a propensity score covariate. The following covariates were included in the first model: diabetes mellitus, randomization to treatment with UFH plus a GPI or bivalirudin, and current smoking. These covariates were selected because of their previously described clinical relationship to ST (9). Additionally, pre-procedural Thrombolysis In Myocardial Infarction (TIMI) flow grade 0/1 (vs. >1), final post-procedural TIMI flow grade 3 (vs. <3), peak creatine phosphokinase, and protocol-defined non-coronary artery bypass graft surgery–related major bleeding were added to the model because of the well-known relationship with mortality after STEMI. The multivariable model was built by stepwise variable selection with entry and exit criteria set at the $p = 0.1$ level. The propensity score was estimated from a logistic regression model for occurrence of in- or out-of-hospital ST. To calculate the propensity score, the following variables were entered into the model: baseline TIMI flow grade 1/0, final TIMI flow grade 3, peak creatine phosphokinase, protocol-defined non-coronary artery bypass graft surgery–related major bleeding, pre-randomization heparin, age, current smoking, randomization to bivalirudin versus UFH plus a GPI, diabetes mellitus,

an advisor for Abbott Vascular. Dr. Brodie is on the Speakers Bureau of The Medicines Co. Dr. Dudek has received research grants or served as a consultant/advisory board memeber for Abbott, Adamed, AstraZeneca, Biotronik, Balton, Bayer, BBraun, BioMatrix, Boston Scientific, Boehringer Ingelheim, Bristol-Myers Squibb, Cordis, Cook, Eli Lilly, EuroCor, Glaxo, Invatec, Medtronic, The Medicines Co., MSD, Nyocomed, Orbus-Neich, Pfizer, Possis, Promed, Sanofi-Aventis, Siemens, Solvay, Terumo, and Tyco. Dr. Witzenbichler has received lecture honoraria from Boston Scientific and The Medicines Co. Dr. Guagliumi has served as a consultant Boston Scientific, St. Jude, Cordis, and Volcano; has received lecture honoraria from Boston Scientific, Medtronic, Lightlab, and Labcoat; and has received grant support from Medtronic, Abbott, Lightlab, and Boston Scientific. Dr. Moses is a consultant for Abbott and Boston Scientific. Dr. Stone is on the scientific advisory boards for and has received honoraria from Abbott Vascular and Boston Scientific; and has served as a consultant to The Medicines Company, Eli Lilly, BMS/Sanofi, and AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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and platelet count (Online Appendix). The propensity score was added as the only covariate in addition to in- versus out-of-hospital ST in the second multivariable Cox model. Formal interaction tests were performed to determine whether diabetes or randomization to bivalirudin versus UFH+GPI affected the relative risk of mortality after in-hospital versus out-of-hospital ST.

Results

Patients and baseline characteristics. Of 3,202 patients in whom stents were implanted, definite/probable ST within 3 years occurred in 156 patients (4.9%). In-hospital ST occurred in 54 patients (34.6%), and out-of-hospital ST occurred in 102 patients (65.4%). The majority of ST events in both groups were definite ST events (46 [85.2%] in-hospital vs. 90 [88.2%] out-of-hospital; p = 0.78). Five patients had 2 ST events each, all of which were definite ST. Two of these patients first had an in-hospital ST, followed 28 and 47 days later by an out-of hospital event; both of these patients were included in the in-hospital ST group. Three patients had 2 out-of-hospital ST events.

The median time to first ST was 1 day (interquartile range: 0 to 5 days] in the in-hospital group and 360 days (interquartile range: 100 to 604 days) in the out-of-hospital group. Mean length of hospital stay was 8.67 ± 6.63 days versus 5.65 ± 5.86 days in the in-hospital versus out-of-hospital groups (p < 0.01).

Baseline clinical and laboratory characteristics in the 2 groups are shown in Table 1. Patients with in-hospital compared with out-of-hospital ST were less frequently diabetic and current smokers, but more frequently had thrombocytopenia. No significant differences were present in other oral medical therapies prescribed before or during the index hospitalization (data not shown), except for beta-blocker use, which was less frequently used during the index hospitalization in patients with in-hospital compared with out-of-hospital ST (83.3% vs. 96.1%, respectively; p = 0.01). Angiographic and procedural characteristics during the index STEMI treatment are summarized in Table 2. In comparison with patients with out-of-hospital ST, those with in-hospital ST more frequently had pre-PCI coronary TIMI flow grade 0/1 and post-PCI coronary TIMI flow grade <3 were more likely to have been randomized to bivalirudin monotherapy, and were less likely to have received pre-randomization heparin. By multivariable analysis, baseline TIMI flow grade 0/1, nonuse of pre-randomization heparin, and randomization to bivalirudin were independent predictors of in-hospital ST, whereas insulin-treated diabetes, prior PCI, cigarette smoking, an elevated platelet count, and randomization to heparin plus a GPI were independent predictors of out-of-hospital ST (Table 3).

Clinical outcomes. As shown in Table 4, the 1-year rates of mortality and major bleeding were higher in patients with in-hospital compared with out-of-hospital definite or probable ST, although the rates of reinfarction were lower. Most of the differences in clinical outcomes (death, myocardial infarction, and bleeding) appeared within 1 week of the ST episode (Fig. 1). The results were similar when only definite ST events were analyzed (Fig. 2); patients with in-hospital compared with out-of-hospital definite ST had significantly

Table 1 Baseline Characteristics of Patients From the Original Index Procedure With In-Hospital and Out-of-Hospital Definite/Probable ST

Variable Description	In-Hospital ST (n = 54)	Out-of-Hospital ST (n = 102)	p Value
Age, yrs	56.5 (50.5, 65.0)	59.0 (52.2, 67.4)	0.26
Male	68.5% (37/54)	80.4% (82/102)	0.10
Body mass index, kg/m^2	28.3 (24.8, 31.0)	27.4 (24.7, 29.8)	0.65
History of hypertension	51.9% (28/54)	58.8% (60/102)	0.40
History of hyperlipidemia	46.3% (25/54)	50.0% (51/102)	0.66
Current smoking	50.0% (27/54)	66.3% (67/101)	0.047
History of diabetes mellitus	11.1% (6/54)	24.5% (25/102)	0.046
Insulin treated	5.6% (3/54)	13.7% (14/102)	0.12
History of prior myocardial infarction	13.0% (7/54)	17.6% (18/102)	0.45
History of prior percutaneous coronary intervention	14.8% (8/54)	21.6% (22/102)	0.31
History of prior coronary artery bypass grafting	1.9% (1/54)	1.0% (1/102)	1.00
History of congestive heart failure	3.7% (2/54)	5.9% (6/102)	0.72
History of peripheral vascular disease	3.7% (2/54)	7.8% (8/102)	0.50
History of renal insufficiency	5.6% (3/54)	4.9% (5/102)	1.00
Current dialysis	1.9% (1/54)	2.0% (2/102)	1.00
Creatinine clearance <60 ml/min	16.0% (8/50)	16.3% (15/92)	0.96
Anemia	7.5% (4/53)	13.0% (12/92)	0.31
Thrombocytopenia*	13.0% (7/54)	3.0% (3/101)	0.03
CPK at hospital admission, U/l	146 (87, 260)	154 (81, 330)	0.98
Peak CPK during original STEMI, U/l	2,218 (1,401, 4,501)	1,510 (540, 3,023)	0.005

Values are median (interquartile range) or % (n/N). *Baseline platelet count <100,000 cells/mm^3.
CPK = creatine phosphokinase; ST= stent thrombosis; STEMI = ST-segment elevation myocardial infarction.

Table 2 Angiographic and Procedural Variables From the Original Index Procedure of Patients With Subsequent In- and Out-of-Hospital Definite/Probable ST

Variable Description	In-Hospital ST (n = 54)	Out-of-Hospital ST (n = 102)	p Value
Door to balloon time, min	86.0 (60.0–124.0)	93.0 (70.0–130.0)	0.50
Symptom onset to balloon time, min	196.5 (161.0–273.5)	224.0 (163.0–375.0)	0.20
Left ventricular ejection fraction	51 (40–60)	50 (40–57)	0.93
Multivessel disease	57.4% (31/54)	58.8% (60/102)	0.86
Number of vessels treated	1.1 ± 0.3	1.0 ± 0.1	0.16
Number of lesions treated	1.3 ± 0.6	1.2 ± 0.4	0.30
Vessel treated			0.48
Left anterior descending coronary artery	39.3% (24/61)	37.1% (39/105)	
Circumflex coronary artery	21.3% (13/61)	11.4% (12/105)	
Right coronary artery	37.7% (23/61)	50.5% (53/105)	
Number of stents implanted	1.8 ± 1.0	1.6 ± 1.1	0.41
Total stent length implanted	24.0 (20.0–44.0)	24.0 (20.0–40.0)	0.47
Post-stent dilation balloon used	39.6% (21/53)	52.5% (52/99)	0.13
Direct stenting	28.0% (14/50)	39.0% (39/100)	0.18
Any drug-eluting stent	71.2% (37/52)	72.0% (72/100)	0.91
Side-branch lesion treated	3.7% (2/54)	6.9% (7/102)	0.72
Aspiration catheter used	9.3% (5/54)	13.7% (14/102)	0.42
Pre-PCI TIMI flow grade 0/1	80.3% (49/61)	64.8% (68/105)	0.03
Final post-PCI TIMI flow grade 3	83.6% (51/61)	93.3% (98/105)	0.046
Post-PCI myocardial blush grade (dynamic)			0.11
Blush 0/1	31.4% (16/51)	18.6% (19/102)	
Blush 2	27.5% (14/51)	23.5% (24/102)	
Blush 3	41.2% (21/51)	57.8% (59/102)	
Randomized to bivalirudin	64.8% (35/54)	39.2% (40/102)	0.002
Pre-randomization heparin	46.3% (25/54)	64.7% (66/102)	0.03
Pre-PCI clopidogrel loading dose given, any dose	94.4% (51/54)	97.1% (99/102)	0.42
600 mg clopidogrel loading dose	54.9% (28/51)	58.6% (58/99)	0.52
300 mg clopidogrel loading dose	45.1% (23/51)	40.4% (40/99)	0.67
Dissection	3.8% (2/52)	2.0% (2/101)	0.61
Thienopyridine prescribed at discharge	97.5% (39/40)	99.0% (101/102)	0.49
Aspirin prescribed at discharge	97.5% (39/40)	98.0% (100/102)	0.66
Aspirin and thienopyridine prescribed at discharge	95.0% (38/40)	98.0% (100/102)	0.32

Values are median (interquartile range), % (n/N), or mean ± SD.
PCI = percutaneous coronary intervention; ST = stent thrombosis; TIMI = Thrombolysis In Myocardial Infarction.

higher 1-year mortality (15.2% vs. 2.3%; $p < 0.01$) and major bleeding (23.5% vs. 6.7%; $p < 0.01$), with lower rates of MI (65.5% vs. 82.2%; $p = 0.03$).

Table 3 Multivariate Predictors of In-Hospital and Out-of-Hospital Definite/Probable Stent Thrombosis

Variable	Odds Ratio	p Value
In-hospital definite/probable ST		
Bivalirudin (vs. UFH+GPI)	1.88 (1.04–3.39)	0.04
Pre-procedural TIMI flow grade 0/1 versus flow grade 2/3	6.36 (2.28–17.73)	0.0004
Pre-randomization heparin	0.46 (0.26–0.80)	0.006
Out-of-hospital definite/probable ST		
Bivalirudin (vs. UFH+GPI)	0.65 (0.43–0.98)	0.04
Insulin-treated diabetes	4.29 (2.36–7.80)	<0.0001
Baseline platelet count (per 10^3 cells/mm^3)	1.00 (1.00–1.01)	0.002
Prior PCI	2.52 (1.54–4.12)	0.0002
Current smoker	2.43 (1.58–3.73)	<0.0001

PCI = percutaneous coronary intervention; ST = stent thrombosis; TIMI = Thrombolysis In Myocardial Infarction; UFH+GPI = unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor.

Subgroup analysis indicated that within the in-hospital ST group, mortality after acute ST was 7.1% and after subacute ST was 50% ($p = 0.0004$). Within the out-of-hospital ST group, mortality was 27.6% after subacute ST, 3.3% after late ST, and 8.0% after very late ST ($p = 0.02$). Detailed data on baseline clinical and angiographic characteristics as well as clinical outcome after acute, subacute, late, or very late ST are included in the Online Appendix.

By multivariable analysis, in-hospital (compared with out-of-hospital) definite/probable ST was a powerful independent predictor of mortality (Table 5). Diabetes was also associated with increased mortality after an ST event, whereas randomization to bivalirudin (as opposed to UFH+GPI) was associated with improved survival after an ST event (Table 4, Fig. 4). Multivariate models for in- versus out-of-hospital definite ST demonstrated directionally similar results to those for definite/probable ST (Table 5).

Table 4 1-Year Clinical Outcomes in Patients With In-Hospital Versus Out-of-Hospital Definite/Probable Stent Thrombosis

Variable Description	In-Hospital ST (n = 54)	Out-of-Hospital ST (n = 102)	p Value
Death	27.8% (15)	10.8% (11)	0.007
Cardiac	27.8% (15)	9.8% (10)	0.004
Noncardiac	0.0% (0)	1.1% (1)	0.51
Reinfarction	56.6% (30)	77.5% (79)	0.005
Q-wave	49.4% (26)	60.8% (62)	0.15
Non–Q-wave	11.9% (6)	20.9% (21)	0.17
Death or reinfarction	74.1% (40)	83.3% (85)	0.16
Stroke	7.6% (3)	2.0% (2)	0.16
Target vessel revascularization	83.3% (45)	80.4% (82)	0.47
Non–target vessel revascularization	23.5% (12)	21.0% (21)	0.69
Major bleeding (non–CABG related)	21.2% (10)	6.0% (6)	0.006
Major bleeding (including CABG related)	23.2% (11)	7.0% (7)	0.005

Event rate percentages are Kaplan-Meier estimates (n).

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; ST = stent thrombosis; TIMI = Thrombolysis In Myocardial Infarction; UFH+GPI = unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor.

Discussion

With 156 ST events, the present study is 1 of the largest to analyze the relationship between ST and subsequent mortality. We observed that in patients with STEMI undergoing primary PCI with stent implantation, more than one-third of all ST events during the 3-year follow-up period occurred during the hospital phase, shortly after the index procedure. One-year mortality after ST was significantly higher in patients with in-hospital compared with out-of-hospital ST, despite more rapid access to care and similar rates of target lesion revascularization. The occurrence of in-hospital compared with out-of-hospital definite or probable ST was an independent predictor of greater mortality after multivariate adjustment, both with and without the use of a propensity score. In-hospital compared with out-of-hospital ST was also associated with greater rates of major bleeding, but fewer myocardial infarctions.

In the present analysis, despite being distanced from immediate clinical care, out-of-hospital ST was associated with lower subsequent 1-year mortality than in-hospital ST.

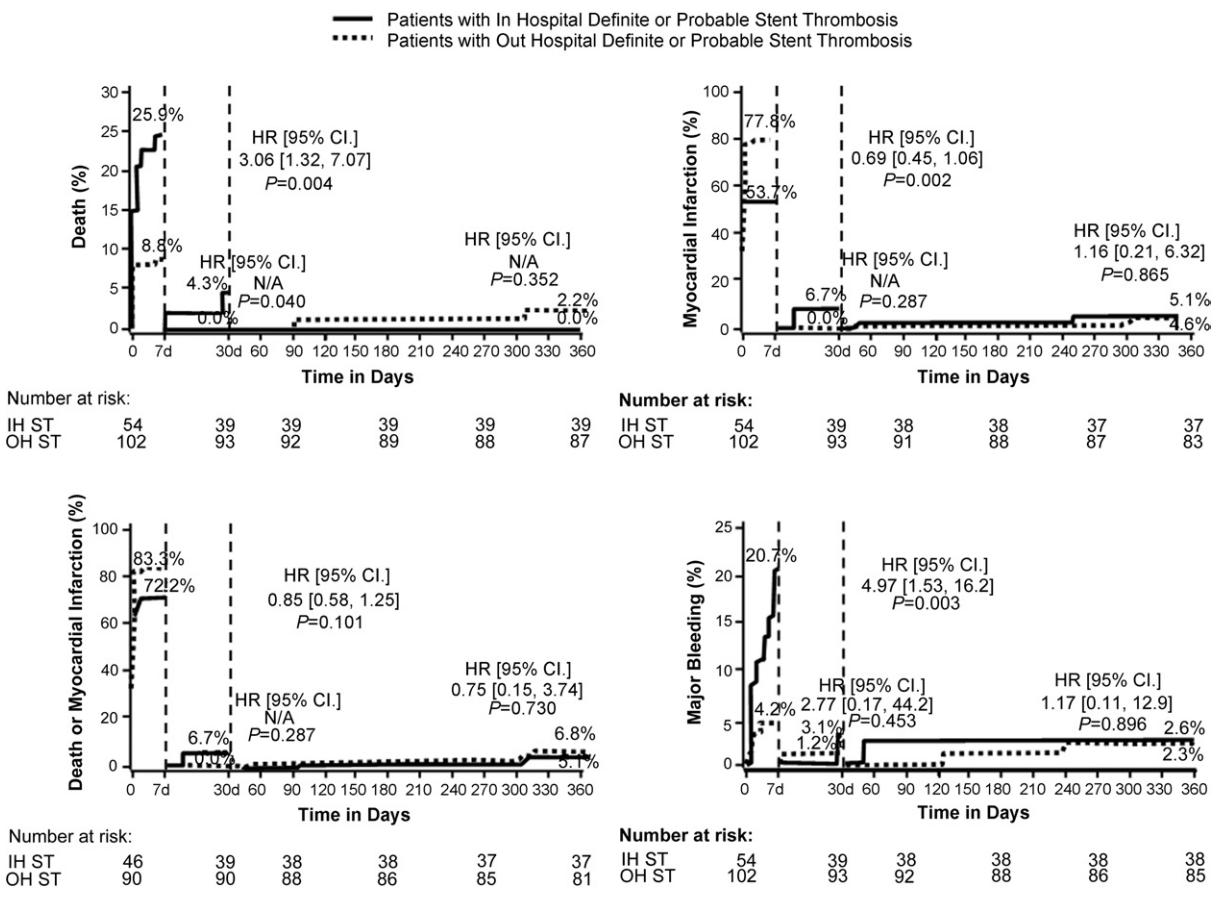

Figure 1 Time-to-Event Curves to 1-Year Follow-Up With Landmarks Set at 7 Days and 30 Days of Clinical Outcome After In- Versus Out-of-Hospital Definite/Probable Stent Thrombosis

Event rates during 0 to 7 days, 8 to 30 days, and 31 days to 1-year intervals after the ST event.
C.I. = confidence interval; HR = hazard ratio; IH = in-hospital; OH = out-of-hospital; ST = stent thrombosis.

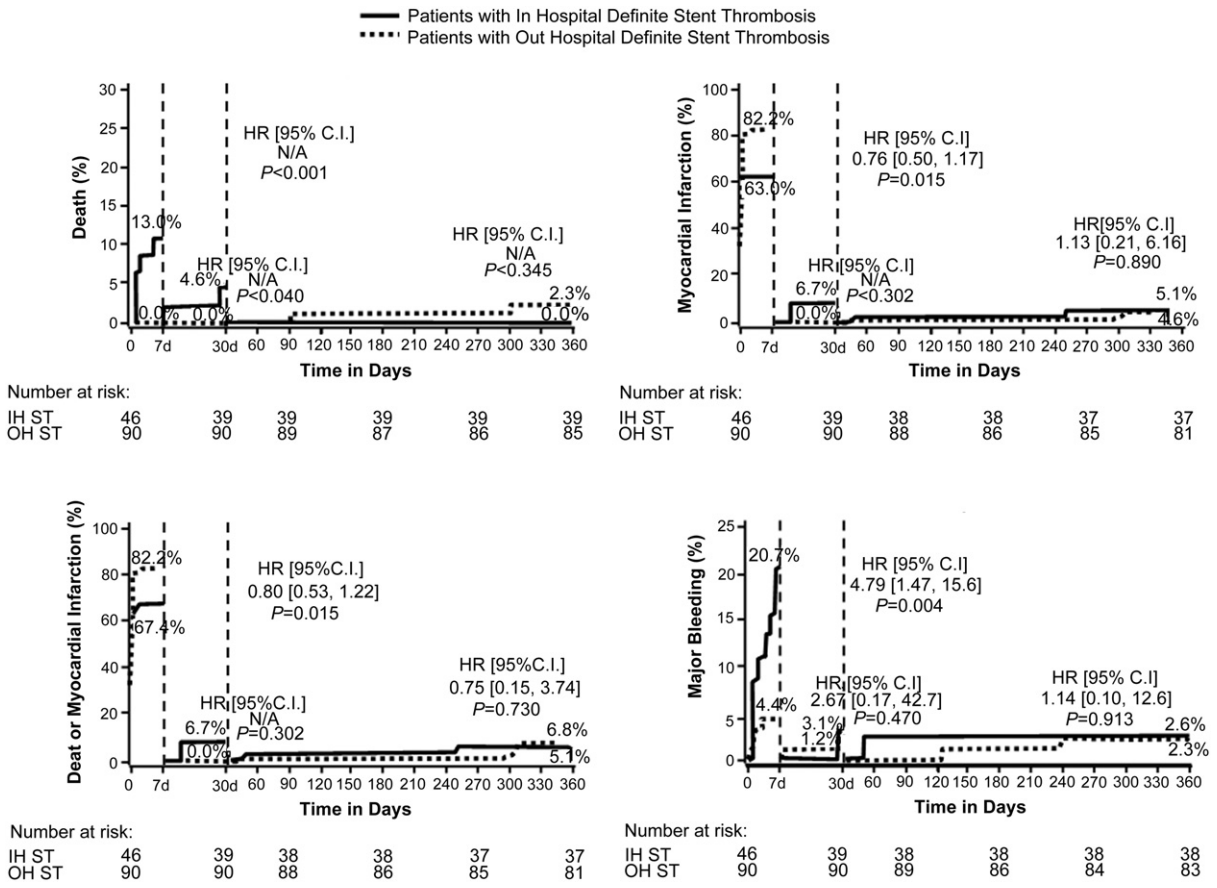

Figure 2 **Time-to-Event Curves to 1-Year Follow-Up With Landmarks Set at 7 Days and 30 Days of Clinical Outcome After In- Versus Out-of-Hospital Definite Stent Thrombosis**

Event rates during 0 to 7 days, 8 to 30 days, and 31 days to 1-year intervals after the ST event. Abbreviations as in Figure 1.

Importantly, the results were similar when only angiographically confirmed definite ST was considered, which eliminates any possible confounding by the inclusion of unexplained deaths within probable ST as defined by the Academic Research Consortium criteria. Thus, early ST after primary PCI in STEMI may portend a particular poor prognosis, presumably due to the incremental loss of myocardium, than in patients with ST after an elective stent procedure. These findings are consistent with a report by Lasala et al., who studied 184 patients with ST after paclitaxel-eluting stent implantation (10). Mortality was higher after acute (29.4%) or subacute ST (41.7%) compared with late (12%) or very late ST (13%). In contrast, the RESTART (Registry of Stent Thrombosis for Review and Reevaluation) investigators reported similar rates of 1-year mortality in patients with acute or subacute ST (22.4%) and late ST (23.5%), although mortality was less frequent in patients with very late ST (10.5%) (2).

Major bleeding has been shown to be a powerful independent predictor of subsequent mortality (11,12), and the higher rates of major bleeding in patients with in-hospital compared with out-of-hospital ST may have contributed to the greater mortality of early ST. A recent subanalysis from the HORIZONS-AMI study reported an unadjusted association between in-hospital major bleeding after STEMI PCI and ST at 3-year follow-up (13). Indeed, occurrence of major bleeding characterizes an overall high-risk patient group. This reflects a population-based observation and should not be construed as a statement implying a causal relationship between bleeding and subsequent ST. In fact, multivariate Cox proportional hazards analysis in the present study did not find in-hospital stent thrombosis to be related to a preceding bleeding event. The question of whether bleeding causes ST, by triggering the coagulation cascade and activating platelets, or whether treatment of ST with femoral reinstrumentation, and antithrombotic and antiplatelet therapy, leads to bleeding is difficult to answer. Alternatively, it is not unthinkable that subclinical bleeding may have led to platelet activation, precipitating ST, with subsequent escalation of bleeding as a result of the treatment for ST. Further study is required in order to answer this question with confidence.

Conversely, it may be supposed that the lower rate of reinfarction in patients with in-hospital ST would be

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Table 5 Adjusted Hazard Ratios for 1-Year Mortality Following In- Versus Out-of-Hospital Stent Thrombosis Adjusted for Selected Covariates (Model 1) and Propensity Score (Model 2)

	HR (95% CI)	p Value
Definite/probable ST		
Multivariate model 1		
In-hospital ST versus out-of-hospital ST	4.62 (1.98–10.77)	0.0004
Current smoking	0.44 (0.20–0.98)	0.04
Final post-PCI TIMI flow grade 3	0.27 (0.11–0.67)	0.004
Bivalirudin versus heparin plus GPI	0.13 (0.05–0.37)	0.0001
Multivariate model 2		
In-hospital ST versus out-of-hospital ST	5.75 (2.37–13.97)	0.0001
Propensity score	0.04 (0.01–0.26)	0.001
Definite ST		
Multivariate model 1		
In-hospital ST versus out-of-hospital ST	40.02 (4.56–351.3)	0.0009
Peak CPK	1.37 (1.03–1.82)	0.0315
Diabetes mellitus	29.46 (2.80–309.4)	0.0048
Bivalirudin versus heparin plus GPI	0.02 (0.00–0.26)	0.0021
Multivariate model 2		
In-hospital ST versus out-of-hospital ST	16.25 (2.83–93.29)	<0.0001
Propensity score	0.03 (0.00–0.72)	0.004

CABG = coronary artery bypass grafting; CI = confidence interval; CK = creatine phosphokinase; HR = hazard ratio; PCI = percutaneous coronary intervention; ST = stent thrombosis; TIMI = Thrombolysis In Myocardial Infarction.

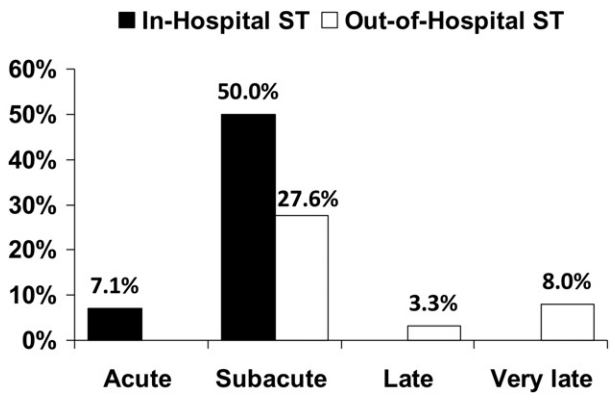

Figure 3 1-Year Mortality According to Academic Research Consortium Timing Definitions

ST = stent thrombosis.

protective from death (11,12). Differences in the underlying pathophysiological mechanism may also be partly responsible for the differences of in-and out-of-hospital ST on mortality. During the early phase, technical and procedural factors are important predictors of ST (1,14,15), whereas delayed neointimal coverage and ongoing vessel inflammation are associated with late ST (16).

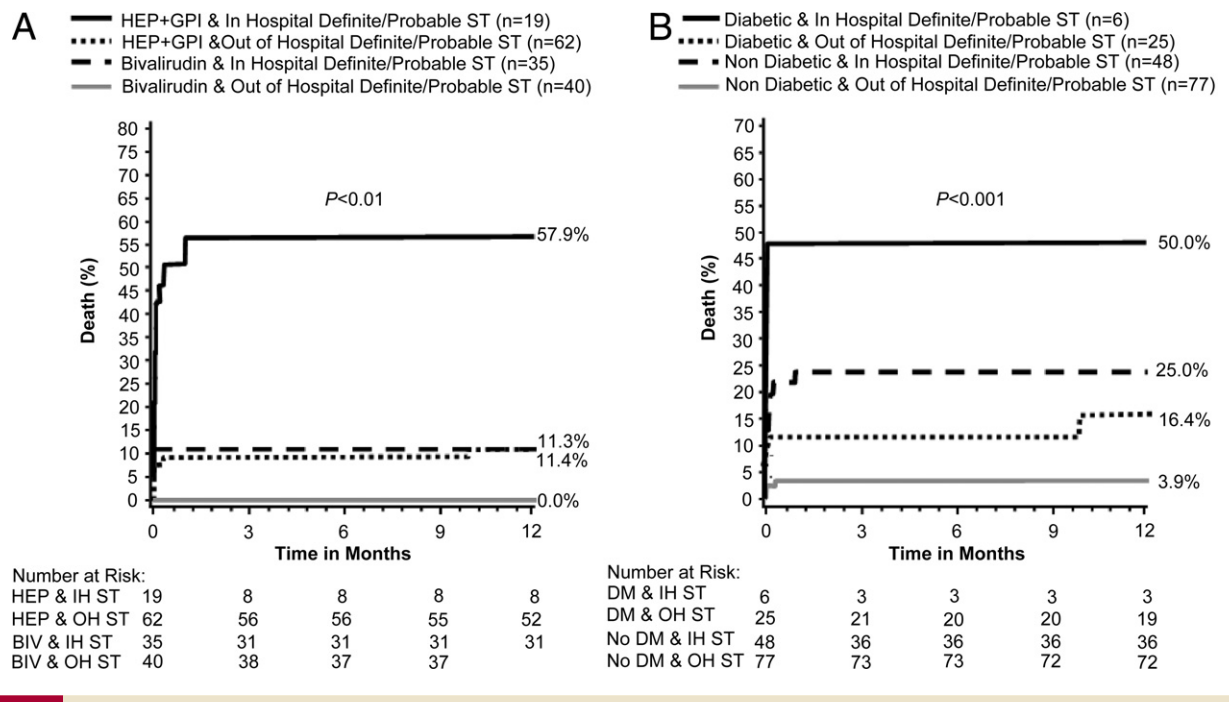

Figure 4 Time-to-Event Curves for Mortality After In- Versus Out-of-Hospital Stent Thrombosis According to Randomization to Bivalirudin Versus Heparin Plus a GPI and the Presence or Absence of Diabetes Mellitus

(A) Bivalirudin versus heparin plus a GPI and **(B)** the presence or absence of diabetes mellitus. A borderline interaction was present between randomization arm and ST type on subsequent mortality (p_{int} = 0.086) but not for diabetes (p_{int} = 0.56). BIV = bivalirudin; DM = diabetes mellitus; GPI = glycoprotein IIb/IIIa inhibitor; HEP = heparin; other abbreviations as in Table 1.

In the present study survival after ST was also worse in patients with diabetes, whereas use of bivalirudin (as opposed to heparin plus a GPI) was associated with lower mortality after ST. The favorable effect of bivalirudin was principally present in patients with in-hospital ST, whereas the effect of diabetes did not have any interaction with the previous variables. Thus, despite the higher rate of acute ST with bivalirudin compared with heparin plus a GPI in STEMI patients undergoing primary PCI (7), the impact of ST on mortality may be less severe when it occurs early after bivalirudin. While the reason for this observation is unknown (and the play of chance cannot be excluded), it may be due to the reduced rate of major bleeding with bivalirudin compared to heparin plus GPI (especially because bleeding complications were increased in patients with in-hospital compared to out-of-hospital ST).

Study limitations. This study was a retrospective analysis from a randomized trial and as such should be considered exploratory. We did not have any information on antiplatelet hyporesponsiveness or related genotypes. Intravascular ultrasound imaging was scarce, not enabling evaluation of the role of angiographically "silent" events such as stent malapposition, underexpansion, or edge dissection. The fact that the original stent implantation was performed during STEMI may have contributed not only to the high rates of early and late stent thrombosis, and may also have relatively worsened the outcome of early versus late ST. Further studies are required to determine whether an early in-hospital ST event may be less catastrophic in patients undergoing elective stent implantation. (Fig 3).

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Key Words: PCI ■ STEMI ■ stent thrombosis.

APPENDIX

For supplemental tables, please see the online version of this article.