Primary Percutaneous Coronary Intervention and Risk of Stent Thrombosis: A Look Beyond the HORIZON

Lorenz Räber and Stephan Windecker

Circulation. 2011;123:1709-1712; originally published online April 11, 2011;
doi: 10.1161/CIRCULATIONAHA.111.023366
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Editorial

Primary Percutaneous Coronary Intervention and Risk of Stent Thrombosis

A Look Beyond the HORIZON

Lorenz Räber, MD; Stephan Windecker, MD

Primary percutaneous coronary intervention (PCI) is the preferred treatment for patients with ST-segment elevation myocardial infarction (STEMI) owing to improved vessel patency, decreased infarct size, lower rates of reinfarction, and improved survival compared with pharmacological reperfusion. However, stent thrombosis (ST) remains a major concern among STEMI patients with an excess 3- to 4-fold increased risk compared with PCI in an elective setting. In the present issue of *Circulation,* the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial investigators provide a detailed report of the incidence, timing, and predictors of ST, specifically addressing the impact of stent type and antithrombotic regimen through 2 years.[1] Definite or probable ST was common (4.4%), with little more than half of events falling into the early period (<30 days), and the remainder being observed in the late period (up to 2 years), without apparent differences in terms of stent type and antithrombotic regimen.

Primary Percutaneous Coronary Intervention and Stent Type

A recent systematic review comparing outcomes between drug-eluting stents (DES) and bare-metal stents (BMS) reported a 56% lower risk of repeat revascularization in favor of DES without differences in terms of death, MI, and ST.[2] A number of registry data extend the benefit of DES to more unselected patients undergoing primary PCI in routine clinical practice. Notwithstanding, there remains a nagging concern about the safety of DES in STEMI patients, particularly during long-term follow-up. What are the principal reasons underlying this clinical equipoise?

Article see p 1745

First, very late ST has been recognized as a distinct entity complicating the use of DES, particularly in the off-label setting. Along this line, observational studies have reported an increased risk of very late ST with DES compared with BMS among STEMI patients.[3,4] Second, none of the individual STEMI trials have been powered adequately to address infrequent adverse events, such as very late ST. Third, histopathological analysis of autopsy specimens revealed more inflammation, fibrin deposition, and uncovered struts among lesions treated with DES in STEMI patients compared with those with stable lesions, suggesting a differential arterial response to DES depending on underlying plaque morphology.[5] Fourth, late acquired stent malapposition (LASM) was more common among DES (31%) than BMS (8%, $P=0.02$) 13 months after PCI in the Intravascular Ultrasound (IVUS) substudy of HORIZONS-AMI.[6] Although it remains a matter of debate whether LASM is causally related to very late ST, LASM in the presence of vessel remodeling is presumably caused by extensive inflammation elicited by DES and highly prevalent among patients presenting with very late ST (75%).[7] Because LASM is a dynamic process and only appears over time, it may become clinically apparent only during very long-term follow-up. The notion of a differential healing response between DES and BMS among STEMI patients is further substantiated by the Optical Coherence Tomography (OCT) substudy of HORIZONS-AMI, which observed a higher rate of uncovered and malapposed struts among DES-treated lesions at 13 months, a pattern much like the one observed in autopsy reports.[8]

Despite the differential healing pattern between DES and BMS, as evidenced in intracoronary imaging and autopsy studies, Dangas et al in this issue of *Circulation* report a similar risk of ST at all time points with the use of paclitaxel-eluting stents and BMS during the 2-year follow-up of HORIZONS-AMI. These seemingly contradictory observations may be due to lack of a true cause–effect relationship between imaging findings and clinical outcome, or due to insufficient power and lack of extended follow-up to detect low-frequency adverse events such as ST. The first concern can only be resolved by adequately designed studies with serial use of intracoronary imaging to investigate the putative role of surrogate markers. To address the second concern, and in an attempt to look beyond the HORIZON, it is worthwhile to analyze the time dependence of the risk of ST in available STEMI trials comparing DES with BMS during the longest available follow-up (Table). Although the risk of ST appears somewhat reduced among DES-treated patients during the first year, the frequency of very late ST is higher in most of the trials compared with BMS at the maximal duration of follow-up. Against this background, it is tempting to hypothesize the following paradigm: DES exert a beneficial effect among STEMI patients by reducing the risk of MI and ST during the first year, an effect that is potentially related to anti-inflammatory properties of the eluted therapeutic agent.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Department of Cardiology and Clinical Trials Unit, Bern University Hospital, Bern, Switzerland.

Correspondence to Stephan Windecker, MD, Professor and Chief of Cardiology, Department of Cardiology, Bern University Hospital, 3010 Bern, Switzerland. E-mail stephan.windecker@insel.ch

(*Circulation*. 2011;123:1709-1712.)

***Circulation* is available at http://circ.ahajournals.org**
DOI: 10.1161/CIRCULATIONAHA.111.023366

Table. Definite and Definite or Probable Stent Thrombosis in 9 Randomized Controlled STEMI Trials Comparing DES With BMS During Long-Term Follow-Up

Trial Acronym	Registration	No. of Patients	Longest Follow-Up, y	Publication or Congress	Definite ST, 0 to 1 y, n (%)	Definite ST, >1 y, n (%)	Definite ST Overall, n (%)	Definite or Probable ST, 0 to 1 y, n (%)	Definite or Probable ST, >1 y, n (%)	Definite or Probable ST Overall, n (%)
DEDICATION	NCT00192868	313 vs 313 (DES vs BMS)	3	*J Am Coll Cardiol.* 2010;56:641–645	3 (1.0) vs 7 (2.2)	2 (0.6) vs 3 (1.0)	5 (1.6) vs 10 (3.2)	NA	NA	9 (2.9) vs 10 (3.2)
HORIZON	NCT00433966	2238 vs 744* (PES vs BMS)	3	TCT, Washington DC, September 27, 2010	58 (2.6) vs 22 (3.0)	36 (1.6) vs 6 (0.8)	94 (4.2) vs 28 (3.7)	70 (3.2) vs 25 (3.4)	37 (1.7) vs 7 (0.9)	107 (4.8) vs 32 (4.3)
MISSION	ISRCTN62825862	158 vs 152 (SES vs BMS)	3	*Am J Cardiol.* 2010;106:4–12	1 (0.6) vs 1 (0.7)	3 (1.9) vs 0	4 (2.5) vs 1 (0.7)	2 (1.3) vs 3 (2.0)	3 (1.9) vs 0	5 (3.2) vs 3 (2.0)
PASSION	ISRCTN65027270	310 vs 309 (PES vs BMS)	5	*JACC Cardiovasc Interv.* 2011;4:24–29.	3 (1.0) vs 3 (1.0)	8 (2.6) vs 2 (0.6)	11 (3.5) vs 5 (1.6)	4 (1.3) vs 7 (2.3)	8 (2.6) vs 3 (1.0)	12 (3.9) vs 10 (3.2)
SESAMI	NCT00288210	160 vs 160 (SES vs BMS)	3	*J Am Coll Cardiol.* 2010;55:810–814	2 (1.3) vs 1 (0.6)	1 (0.6) vs 1 (0.6)	3 (1.9) vs 2 (1.3)	NA	NA	NA
MULTI STRATEGY	NCT00229515	372 vs 372 (SES vs BMS)	3	ESC Stockholm, Sweden, August 29, 2010	9 (2.4) vs 11 (3.0)	3 (0.8) vs 2 (0.5)	13 (3.5) vs 13 (3.5)	10 (2.7) vs 15 (4.0)	5 (1.3) vs 2 (0.5)	15 (4.0) vs 17 (4.0)
TYPHOON	NCT00232830	355 vs 357 (SES vs BMS)	4	*JACC Cardiovasc Interv.* 2011;4:14–23	4 (1.6) vs 8 (3.2)	5 (2.0) vs 2 (0.8)	9 (3.6) vs 10 (4.0)	6 (2.4) vs 9 (3.6)	5 (2.0) vs 3 (1.2)	11 (4.4) vs 12 (4.8)
PASEO	NCT00759850	90 vs 90 vs 90 (SES vs PES vs BMS)	4	*Am Heart J.* 2009;158:43–50	1 (1.1) vs 1 (1.1) vs 1 (1.1)	0 vs 0 vs 0	1 (1.1) vs 1 (1.1) vs 1 (1.1)	2 (2.2) vs 2 (2.2) vs 2 (2.2)	1 (1.1) vs 2 (2.2) vs 4 (4.4)	3 (3.3) vs 4 (4.4) vs 6 (6.7)
STRATEGY	NCT00229515	88 vs 88 (SES vs BMS)	5	*J Am Coll Cardiol.* 2010;55:810–814	0 vs 2 (2.2)	0 vs 0	2 (2.2) vs 2 (2.2)	1 (1.1) vs 4 (4.5)	0 vs 0	1 (1.1) vs 4 (4.5)

Not all publications reported both absolute event rates and percentages. In case only absolute event rates were available, we divided the absolute event No. by the No. of patients at risk at the time of inclusion. In case only percentages were available, we derived the absolute event numbers of events by multiplying the percentage with the No. of patients at risk at baseline.

*In HORIZON, patient No. at risk for ST at baseline is different compared to the patient No. at risk for the primary outcome.

ST indicates stent thrombosis; DEDICATION, Drug Elution and Distal Protection in Acute Myocardial Infarction; DES, drug-eluting stent; BMS, bare metal stent; NA, not applicable; HORIZONS, Harmonizing.

Outcomes With Revascularization and Stents in Acute Myocardial Infarction; PES, paclitaxel-eluting stent; TCT, Trancatheter Cardiovascular Therapeutics Congress; MISSION, A Prospective Randomised Controlled Trial to Evaluate the Efficacy of Drug-Eluting Stents versus Bare-Metal Stents for the Treatment of Acute Myocardial Infarction; SES, siroliumus-eluting stent; PASSION, Paclitaxel-Eluting Versus Conventional Stent in Myocardial Infarction With ST-Segment Elevation; SESAMI, Sirolimus-Eluting Stent in Acute Myocardial Infarction; MULTI STRATEGY, Multicenter Evaluation of Single High-Dose Bolus Tirofiban versus Absicximab with Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction Study; TYPHOON, Trial to Assess the Use of the CYPHer Sirolimus-Eluting Coronary Stent in Acute Myocardial Infarction Treated With BallOON Angioplasty; PASEO, Paclitaxel- or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty; and STRATEGY, Tirofiban and Sirolimus-Eluting Stent vs Abciximab and Bare-Metal Stent for Acute Myocardial Infarction.

This beneficial effect may be subsequently offset (beyond 1 year) by proinflammatory properties of the polymer matrix, resulting in hypersensitivity reactions or chronic inflammation of the treated segment.

Although all studies among STEMI patients performed to date used early generation DES, newer generation DES with durable and biodegradable polymer-based drug release may provide the basis for improved biocompatibility and vascular healing. Two ongoing trials investigate newer generation DES in the setting of STEMI: Clinical Evaluation of Everolimus Eluting Coronary Stents in the Treatment of Patients With ST-segment Elevation Myocardial Infarction (EXAMINATION; NCT 00828087) compares everolimus-eluting stents with BMS in 1504 STEMI patients, whereas Comparison of Biolimus Eluted From an Erodable Stent Coating With Bare-Metal Stents in Acute ST-Elevation Myocardial Infarction (COMFORTABLE AMI; NCT 00962416) compares a stent releasing biolimus A9 from a biodegradable polymer with BMS in 1,159 STEMI patients. If newer generation DES maintain the early benefit compared with BMS while simultaneously eliminating the late adverse event profile, an important progress in the treatment of STEMI patients could appear on the HORIZON.

Primary Percutaneous Coronary Intervention and Antithrombotic Regimen

ST-segment elevation myocardial infarction is mostly caused by rupture of inflamed plaques with exposure of the thrombogenic lipid-rich core, resulting in platelet aggregation and tissue factor-mediated activation of the coagulation cascade with thrombin generation. Unlike unfractionated (UFH) and low–molecular-weight heparin, direct thrombin inhibitors block not only soluble, but also clot-bound, thrombin, which is the theoretical underpinning of the more specific, and potentially more effective, profile of these agents. In this context, HORIZONS-AMI compared an antithrombotic strategy of bivalirudin monotherapy with the combined use of UFH plus a glycoprotein IIb/IIIa antagonist among STEMI patients. Although the 2-year cumulative incidence of ST was similar for both antithrombotic regimens, acute ST was more common among patients treated with bivalirudin, and bivalirudin use emerged as a strong independent predictor of acute ST. A few limitations are notable, including the open-label design, the administration of UFH before randomization in > two thirds of patients, and the variable clopidogrel loading dose. Moreover, it is arguable whether late and very late ST are in any way related to the periprocedural antithrombotic regimen. Of note, the 1.1% incremental risk of acute ST with bivalirudin monotherapy must be weighed against its benefits and overall clinical outcome. Thus, bivalirudin monotherapy compared with UFH plus glycoprotein IIb/IIIa antagonists was associated with a significant decrease in major bleeding and, more importantly, a significantly lower mortality at 30 days and 1 year, presumably because of fewer deaths from bleeding causes, rendering the excess mortality in acute ST inconsequential.

Two observations emerge from the present study, which may provide guidance in the search for the most effective periprocedural antithrombotic regimen. First, prerandomization use of UFH was a strong predictor of freedom from acute ST, and lowered its risk by 73%. This finding may point to the importance of more potent and prolonged thrombin inhibition. Because of its short half-life, the antithrombotic effects of bivalirudin are quickly reversible, but may uncover residual thrombin activity, which may play a role in the genesis of recurrent ischemic events. The prolonged administration (median 7 days) of low–molecular-weight heparin was more effective than a short duration of UFH (median 2 days) in the prevention of death and MI among STEMI patients included in the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment—Thrombolysis in Myocardial Infarction 25 (ExTRACT-TIMI 25) trial.[9] The difference only emerged at the time of discontinuation of UFH, suggesting that a prolonged antithrombin regimen is beneficial. One therapeutic option to mitigate the increased risk of acute ST could therefore be a prolonged infusion of bivalirudin after PCI in STEMI patients, even though this strategy may abrogate the advantage of a lower bleeding risk.

Second, use of high-dose (600 mg) clopidogrel loading was a strong predictor of freedom from subacute ST. The higher loading dose affords more rapid and greater inhibition of platelet aggregation than the standard (300 mg) regimen, and reduced the risk of subacute ST by 48% in the present study. Similar findings have been observed in the Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for Interventions (CURRENT OASIS 7) trial,[10] with a 46% lower risk of definite ST after a high- rather than a standard-dose clopidogrel regimen among patients with acute coronary syndromes undergoing PCI. Of note, the protective effect of high-dose clopidogrel to prevent ST in the present study was restricted to the subacute phase and not apparent during the acute phase, highlighting the delayed onset of action of this type of oral P2Y12 inhibitor. This shortcoming may be overcome by newer antiplatelet agents with more rapid, intense, and consistent inhibition of platelet aggregation. Compared with high loading dose clopidogrel, prasugrel as well as ticagrelor achieve a greater degree of platelet inhibition as soon as 30 minutes, which is maintained throughout 24 hours. Moreover, prasugrel and ticagrelor lowered the risk of definite ST compared with clopidogrel by 58% and 33%, respectively, in large-scale clinical trials of acute coronary syndrome patients.[11,12] Accordingly, the combination of prasugrel or ticagrelor with bivalirudin may become an attractive therapeutic option, particularly among STEMI patients, as none of the antiplatelet drugs were associated with an increased risk of bleeding in this patient population.

As is true of any great study, the results of HORIZONS-AMI not only contribute to the current standard of care, but also stimulate numerous important questions and hypotheses. Our blurred look of what appears on the HORIZON will be sharpened by future investigations addressing some of the hypotheses outlined above.

Disclosures

Dr Windecker has received consulting and lecture fees from Abbott, Boston Scientific, Biosensors, Cordis, and Medtronic. Dr Räber reports no conflicts.

References

1. Dangas GD, Caixeta A, Mehran R, Parise H, Lansky AJ, Cristea E, Brodie BR, Witzenbichler B, Guagliumi G, Peruga JZ, Dudek D, Möeckel M, Stone GW. Frequency and predictors of stent thrombosis after percutaneous coronary intervention in acute myocardial infarction. *Circulation.* 2011;123:1745–1756.
2. Brar SS, Leon MB, Stone GW, Mehran R, Moses JW, Brar SK, Dangas G. Use of drug-eluting stents in acute myocardial infarction: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2009;53:1677–1689.
3. Brodie B, Pokharel Y, Fleishman N, Bensimhon A, Kissling G, Hansen C, Milks S, Cooper M, McAlhany C, Stuckey T. 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 Cardiovasc Interv.* 2011;4:30–38.
4. Kukreja N, Onuma Y, Garcia-Garcia H, Daemen J, van Domburg R, Serruys PW. Primary percutaneous coronary intervention for acute myocardial infarction: long-term outcome after bare metal and drug-eluting stent implantation. *Circ Cardiovasc Interv*. 2008;1:103–110.
5. Nakazawa G, Finn AV, Joner M, Ladich E, Kutys R, Mont EK, Gold HK, Burke AP, Kolodgie FD, Virmani R. 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;118:1138–1145.
6. Guo N, Maehara A, Mintz GS, He Y, Xu K, Wu X, Lansky AJ, Witzenbichler B, Guagliumi G, Brodie B, Kellett MA Jr, Dressler O, Parise H, Mehran R, Stone GW. 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;122:1077–1084.
7. Cook S, Ladich E, Nakazawa G, Eshtehardi P, Neidhart M, Vogel R, Togni M, Wenaweser P, Billinger M, Seiler C, Gay S, Meier B, Pichler WJ, Juni P, Virmani R, Windecker S. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation*. 2009;120:391–399.
8. Guagliumi G, Costa MA, Sirbu V, Musumeci G, Bezerra HG, Suzuki N, Matiashvili A, Lortkipanidze N, Mihalcsik L, Trivisonno A, Valsecchi O, Mintz GS, Dressler O, Parise H, Maehara A, Cristea E, Lansky AJ, Mehran R, Stone GW. Strut coverage and late malapposition with paclitaxel-eluting stents compared with bare metal stents in acute myocardial infarction: optical coherence tomography substudy of the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. *Circulation.* 2011;123:274–281.
9. Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M, Sadowski Z, Budaj A, Lopez-Sendon JL, Guneri S, Jiang F, White HD, Fox KA, Braunwald E. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med*. 2006;354:1477–1488.
10. Mehta SR, Tanguay JF, Eikelboom JW, Jolly SS, Joyner CD, Granger CB, Faxon DP, Rupprecht HJ, Budaj A, Avezum A, Widimsky P, Steg PG, Bassand JP, Montalescot G, Macaya C, Di Pasquale G, Niemela K, Ajani AE, White HD, Chrolavicius S, Gao P, Fox KA, Yusuf S. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7). *Lancet*. 2010;376:1233–1243.
11. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015.
12. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med*. 2009;61:1045–1057.

KEY WORDS: Editorials ■ myocardial infarction ■ revascularization ■ stents ■ thrombosis