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?

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

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<table>
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<th>Trial Acronym</th>
<th>Registration</th>
<th>No. of Patients</th>
<th>Longest Follow-Up, y</th>
<th>Publication or Congress</th>
<th>Definite ST, 0 to 1 y, n (%)</th>
<th>Definite ST, &gt;1 y, n (%)</th>
<th>Definite ST Overall, n (%)</th>
<th>Definite or Probable ST, 0 to 1 y, n (%)</th>
<th>Definite or Probable ST, &gt;1 y, n (%)</th>
<th>Definite or Probable ST Overall, n (%)</th>
<th>Definite or Probable ST Overall, n (%)</th>
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<td>2 (0.6) vs 3 (1.0)</td>
<td>2 (0.6) vs 3 (1.0)</td>
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<td>2238 vs 744*</td>
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<td>36 (1.6) vs 6 (0.8)</td>
<td>94 (4.2) vs 28 (3.7)</td>
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<td>1 (1.1) vs 4 (4.5)</td>
<td>1 (1.1) vs 4 (4.5)</td>
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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, Transcatheter 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, sirolimus-eluting stent; PASSION, Paclitaxel-Eluting Versus Conventional Stent in Myocardial Infarction With ST-Segment Elevation; SESAMI, Sirolimus-Eluting Stents in Acute Myocardial Infarction; MULTI STRATEGY, Multicenter Evaluation of Single High-Dose Bolus Tirofiban versus Abciximab 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 BailON 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 1,504 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 Repfusión 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 Antiplaeteat 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


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