Prognostic factors in primary and elective percutaneous coronary intervention
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Chapter 14

Clinical Outcomes Following Stent Thrombosis Occurring In-Hospital versus Out-of-Hospital: results from the HORIZONS-AMI Trial

Submitted

ABSTRACT

Background: We developed and validated a risk score to personalize risk assessment for stent thrombosis (ST) after percutaneous coronary intervention (PCI) for acute coronary syndromes (ACS).

Methods and Results: This study represents a patient-level pooled analysis of 6,139 patients undergoing PCI with stent implantation for ACS in the HORIZONS-AMI and ACUITY trials who were randomized to treatment with bivalirudin versus heparin plus a glycoprotein IIb/IIIa inhibitor. The cohort was randomly divided into a risk score development cohort (n=4093) and a validation cohort (n=2046). Cox regression methods were used to identify clinical, angiographic and procedural characteristics associated with ARC-defined definite/probable ST at 1-year. Each covariate in this model was assigned an integer score based on the regression coefficients. Variables included in the risk score were: type of ACS (STEMI, NSTE-ACS with ST deviation, or NSTE-ACS without ST changes), current smoking, insulin dependent diabetes mellitus, prior PCI, baseline platelet count, absence of early (pre-PCI) anticoagulant therapy, aneurysmal/ulcerated lesion, baseline TIMI 0/1 flow, final TIMI flow grade under 3, and number of treated vessels. Risk score 1-6 was considered low risk, 7-9 intermediate risk, and 10 or greater high risk for ST. Rates of ST at 1-year in low, intermediate and high risk categories were 1.36%, 3.06%, and 9.18%, respectively in the development cohort (p for trend <0.001), and 1.65%, 2.77%, and 6.45% in the validation cohort (p for trend 0.006). The c-statistic for this risk score was over 0.65 in both cohorts.

Conclusion: The individual risk of ST can be predicted with the use of a simple risk score based on clinical, angiographic and procedural variables.

Clinical Trial Registration: HORIZONS-AMI: registered at clinicaltrials.gov  #NCT00433966, ACUITY: registered at clinicaltrials.gov # NCT00093158
INTRODUCTION

Stent thrombosis (ST) is a rare, yet feared complication after percutaneous coronary intervention (PCI) which is associated with high rates of morbidity and mortality reported by several randomized clinical trials and registries. (1-6) A large number of patient-related, lesion-related, procedural, and post-procedural factors have been associated with ST. (1-4,7) Stenting in prothrombotic conditions in patients with acute coronary syndromes (ACS) is strongly associated with the occurrence of ST. (7-9) However, due to the rarity of ST events, systematic ST risk assessment has not been realized at the individual patient level. A risk score for ST after PCI in ACS can be a helpful tool to personalize risk assessment.

In the present study, we aimed to develop and validate a practical risk score for ST based on a pooled analysis of patients undergoing PCI with stent implantation in two prospective randomized clinical trials of patients with ACS. (10,11)

METHODS

This study represents a pooled analysis of patients undergoing PCI with stent implantation in 2 large randomized clinical trials of bivalirudin vs. heparin plus a glycoprotein IIb/IIIa inhibitor (GPI): The HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial of patients with ST-segment elevation myocardial infarction (STEMI), and ACUITY (the Acute Catheterization and Urgent Intervention Triage Strategy trial) trial of patients with unstable angina or non-STEMI. (10,11)

The design and primary outcomes of these trials have been described in detail previously. (11,12) Briefly, in HORIZONS-AMI, 3,602 patients admitted with STEMI presenting within 12 hours after symptom onset were directed to therapy with primary angioplasty and were randomized (1:1) to receive either bivalirudin monotherapy (plus bail-out glycoprotein [GP] IIb/IIIa inhibitor; GPI) or unfractionated heparin plus a GPI before PCI; Following angiography, 3,006 patients were randomized (3:1) to TAXUS Express2 paclitaxel-eluting stents or otherwise identical metallic stents (both Boston Scientific, Natick, Ma). Aspirin and clopidogrel (either 300 mg or 600 mg, at the discretion of the investigator), or ticlopidine (500 mg in the case of allergy to clopidogrel) was administered before catheterization. In ACUITY, eligible patients with unstable angina or non-STEMI were randomly assigned to treatment with bivalirudin, versus bivalirudin plus a GPI, versus heparin (either unfractionated or low molecular weight) plus a GPI before performance of coronary angiography. All patients received aspirin, and timing and dosing of clopidogrel was left to the discretion of investigators and treating physicians. Clinical follow-up was pre-specified at 30 days, 6 months and 1 year in both trials. Extended follow-up up to 3 years was only available in the HORIZONS trial.

The Academic Research Consortium definite or probable ST criteria were used (13), and all ST events were adjudicated using source documents by the independent clinical event committees of the two trials.

Risk score development We randomly divided the pooled dataset in a 2:1 fashion into a development cohort and a validation cohort and considered the 1-year follow-up for the primary analysis since this was the longest common follow-up period for both datasets. Univariate and multivariate analyses for prediction of ST have previously been performed in both individual trials. (14, and Palmerini T., MD, unpublished data, 2011) A Cox proportional hazards model was used to calculate hazard ratios of clinical, angiographic, and procedural variables. Models were built using a stepwise variable selection procedure; a value of p<0.05 was set as the level of significance for including variables in the model. To prevent overfitting, we included co-variates which were independent predictors of stent thrombosis in the individual trials in the model. (14, and Palmerini T., unpublished data, 2011) Slight modifications were made to accommodate differences between the study databases: 1) ST-deviation was classified as STEMI, non-STEMI with ST-deviation ≥1mm, or
ACS without ST-deviation, 2) Pre-randomization administration of antithrombotic medication was associated with ST in HORIZONS, and was generalized to early (pre-PCI) anticoagulant therapy in both trials, 3) angiographic ulceration and aneurysm both were independent predictors of ST in HORIZONS, and were generalized to ulceration or aneurysm, instead of two separate variables. The remaining variables included were: baseline platelet count, current smoking, insulin-treated diabetes mellitus, prior PCI, number of treated vessels, baseline TIMI flow grade 0/1, and final TIMI flow grade under 3. Use of drug-eluting stents compared with bare-metal stents was not associated with ST. Each covariate in this model was assigned an integer score based on the regression coefficients. Integer scores were subsequently summed to give the risk score for each patient. The 1-year rate of ST within each score category was derived per integer score and then per low-intermediate-high risk classification. A significant p-value for trend was considered at the <0.05 level. Overall model performance was assessed with the c-statistic.

Score Validation. To test the validity of the above findings, we investigated the correlation of the derived risk score with the ST rate observed in the validation cohort. The rates of ST per risk score category were derived and compared for trend. Overall model performance was assessed by the c-statistic. A secondary analysis was performed with inclusion of the extended follow-up data of HORIZONS trial (beyond 1 and up to 3 year follow-up) in the validation dataset in order to provide information on prediction of very late ST.

RESULTS

A total of 2,986 patients who received stent implantation after primary PCI in the HORIZONS-AMI trial, and a total of 3,153 patients who underwent PCI with stent placement in the ACUITY trial with complete datasets were included in this patient-pooled analysis (total cohort n=6,139). The majority of patients were treated with at least one DES (n=5,000, n=81.4%). The cohort was then randomly split in a 2:1 fashion into a development (n=4,093) and a validation cohort (n=2,046). There were no differences in baseline clinical, angiographic, and procedural characteristics, and clinical outcomes between patients in the development and validation cohorts (data not shown in paper, available as Appendix for the reviewers). A total of 106 ST events (2.6%) occurred in the development cohort and 50 ST events (2.4%) occurred in the validation cohort.

Development dataset. Variables included in the risk score and their hazard ratios are shown in Table 1. Independent predictors of ST at one year follow-up were: type of ACS (STEMI, NSTE-ACS with ST deviation, or NSTE-ACS without ST changes), current smoking, insulin dependent diabetes mellitus, prior PCI, baseline platelet count, absence of early (pre-PCI) anticoagulant therapy,
ulceration or aneurysm of target lesion, baseline TIMI grade flow 0/1, final TIMI flow grade under 3, and number of treated vessels.

Table 2 shows the corresponding integer assignments and calculation of the risk score. Each variable was assigned a +1 to +4 score according to the strength of the statistical association. The distribution of the integer risk score and consequent probability of ST at 1-year is shown in Figure 1, upper panels (p-value for trend < 0.0001). The c-statistic for the risk score was 0.67 in the development cohort. From observation of these data, 3 categories of ST risk might arbitrarily be defined: risk score 1-6 was considered low risk, 7-9 intermediate risk, and 10 or greater high risk for ST. Rates of ST in low, intermediate, and high-risk groups are shown in Figure 1, lower panels (p-value for trend, <0.0001).

**Score Validation.** Figure 2 (upper panels) shows the distribution of the integer risk score and consequent probability of definite/probable ST at 1 year in the validation cohort. The c-statistic for the ST risk score model in the validation cohort was 0.66. Figure 2 (lower panels) shows the distribution of low, intermediate, and high risk groups, and their corresponding ST rates at 1-year. The ST trends among the 3 risk categories remained significant (p<0.001).

In a secondary analysis, we extended the above validation cohort to also include the data on the extended follow-up of the HORIZONS trial (beyond 1 year and until the 3 year study end) in order to also include a very late ST assessment. The ST rates in the low, intermediate and high risk categories were 2.52%, 4.70%, 12.68%, (p for trend <0.0001) and the c-statistic was 0.69.

**DISCUSSION**

The current analysis in a patient-pooled dataset of two large randomized clinical trials that span the spectrum of ACS resulted in the development and validation of a convenient integer-based risk score consisting of 10 readily available variables. We believe that the development and initial validation of this ST risk score can be a useful tool for both clinical practice and future clinical investigation (future analyses of trials or registries), as it can be a simple way to risk stratify patients immediately post procedure.

In our analyses, we found that most patients were in the low risk categories (Fig 1 and 2, bottom
left panels). This is in accordance with the rarity of ST events and with the great difficulties smaller datasets with less prolonged follow-up would have had in order to perform such an analysis. In addition, we documented highly statistically significant incremental ST rates with increasing risk score integer values in both the development and validation datasets. Finally, we showed the above trends paralleled each other in the derivation and validation cohorts.

The variables of the proposed risk score can be subcategorized into clinical and laboratory, pharmacological, and angiographic variables. Clinical variables include: Type of ACS, prior studies have suggested higher ST rates in STEMI compared with NSTE-ACS, (7,14) moreover, the current investigation reported higher ST rates after NSTE-ACS with ST deviation ≥1mm compared with NSTE-ACS without ST deviation; Insulin-treated diabetes mellitus (previously described as a powerful predictor of subacute, late and very late ST); (6,14) previous PCI, which might indicate prior stent placement and could also signify an index acute coronary syndrome as a result of ST of a previously implanted stent; current smoking, which has been associated with ST in multiple prior studies; (6,14) Additionally, the laboratory value of thrombocytosis has been reported to be associated with ST in an earlier analysis in the HORIZONS-AMI trial. (14)

We previously reported a protective effect of prerandomization use of heparin in the HORIZONS-AMI trial. (14) This important pharmacological variable was generalized as early (pre-PCI) administration of anticoagulant therapy to facilitate the clinical applicability of the current risk score. To be more specific, we mean any early use of a readily available parenteral heparin (either unfractionated or low molecular weight) therapy in the emergency department, ambulance or medical floor well before the start of the PCI procedure. With respect to early use of glycoprotein Ilb/IIIa inhibitors, the ACUITY timing substudy had already shown no difference with respect to clinical outcomes (including ST) of early versus during-PCI administration of these agents. (15,16) With respect to early clopidogrel administration, an earlier report from the same trial found no major difference in outcomes with earlier administration as long as clopidogrel was administered preprocedure. (17) Future investigation of different datasets that may include other potent antiplatelet agents administered at different times before PCI may be able to further identify whether such practices may be protective of ST. (18-20) The present study did not assess the

Figure 1 Distribution of the integer risk score and consequent probability of definite/probable stent thrombosis within 1 year in the derivation cohort
discontinuation of antiplatelet therapy which is a known important modifier of ST risk during the follow-up time (3), since we aimed to derive a risk score for ST based on information available solely at the time of stent implantation procedure.

Angiographic variables of this risk score largely reflect the thrombotic load. A baseline TIMI grade flow of 0 or 1 at the target lesion of an ACS patient signifies an occlusive thrombus at time of PCI, and a final TIMI grade flow under 3 during an acute coronary syndrome generally indicates distal embolization and microvascular impairment from microthrombi and vasoactive substances. Aneurysms or ulcerations at the target lesion site have also been used as indicators of thrombus. All of these parameters have also been associated with unfavorable outcomes in part due to possible misinterpretation of the true vessel size during stent implantation, possibly leading to malapposition. The number of treated vessels during the index PCI procedure during an ACS was also an important risk factor of ST. Finally, thrombus extraction before STEMI angioplasty has been associated with improved outcomes in a single large study. This study was completed after HORIZONS enrollment; the very low rate of aspiration thrombectomy in HORIZONS precluded the meaningful assessment of this variable in the present risk score.

We did not include the type of stent used, because no major difference in ST has been found between BMS and first-generation DES types within the trials we analyzed. This also has been reported by other research groups. Whether newer generation drug eluting stents or other stent designs may impact the incidence of ST, particularly very late ST, remains a question for further investigation. Recent evidence indeed suggests a suppression of ST with a widely studied second-generation DES.

The present risk score was developed and validated in patients with ACS, therefore, it may not be applicable to the large population of patients with elective or non-urgent PCI. It is also possible that other variables such as multilesion/multistent PCI, syntax score, bifurcation anatomy, and lesion or stent length may be preferable for inclusion in a ST risk score for use in an elective/non-urgent PCI population. On the other hand, the present risk score could also be validated in an elective/non-urgent PCI population with simple exclusion of the non-applicable variables or in combination with

**Figure 2** Distribution of the integer risk score and consequent probability of definite/probable stent thrombosis within 1 year in the validation cohort
an angiographic burden/jeopardy score (either for the entire coronary anatomy or of the target areas of the index PCI/stenting).

Limitations. This analysis of ST risk estimation was based on 2 clinical trials, one in patients with STEMI and one in patients with unstable angina or non-STEMI. In these trials, no data were collected on deployment pressure and CYP2C19 alleles. In addition, thrombus extraction before STEMI angioplasty has been associated with improved outcomes, (24) only a small proportion of patients in the ACUITY and HORIZONS-AMI trials received this adjunctive treatment which limited our ability to investigate a potential protective effect. Further validation in different ACS trials and registries conducted by other research groups would be desirable. Finally, further validation in patients undergoing an elective or non-urgent PCI with stent implantation would be ideally done within other large trials or registries conducted in appropriately defined patient populations.

Reference List

ACUITY Timing trial. JAMA. 2007;297:591-602


