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Characterization of the Average Daily Ischemic and Bleeding Risk After Primary PCI for STEMI

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ABSTRACT

BACKGROUND The risk of recurrent ischemic and bleeding events after primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) may not be uniform over time, which may affect the benefit-to-risk ratio of guideline-recommended antithrombotic therapies in different intervals.

OBJECTIVES This study sought to characterize the average daily ischemic rates (ADIRs) and average daily bleeding rates (ADBRs) within the first year after primary PCI for STEMI.

METHODS Among 3,602 patients with STEMI who were enrolled in the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial, all ischemic and bleeding events, including recurrent events, were classified according to the timing of their occurrence as acute (≤24 h after PCI), subacute (1 day to 30 days), and late (30 days to 1 year). Patients were treated with aspirin and clopidogrel for the entire year. ADIRs included cardiac death, reinfarction, and definite stent thrombosis. ADBRs included non–coronary artery bypass graft–related Thrombolysis In Myocardial Infarction major and minor bleeding. ADIRs and ADBRs were calculated as the total number of events divided by the number of patient-days of follow-up in each interval assuming a Poisson distribution. Generalized estimating equations were used to test the absolute least square mean differences (LSMD) between ADIRs and ADBRs.

RESULTS The ADIR and ADBR both exponentially decreased from the acute to the late periods ($p < 0.0001$). Although there were no significant differences in ADIR and ADBR in the acute phase (LSMD: +0.11%; 95% confidence interval [CI]: −0.35% to 0.58%; $p = 0.63$), the ADBR was greater than the ADIR in the subacute phase (LSMD: −0.39%; 95% CI: −0.58% to −0.20%; $p < 0.0001$). In the late phase, the ADIR exceeded the ADBR (LSMD: +1.51%; 95% CI: 1.04% to 1.98%; $p < 0.0001$).

CONCLUSIONS After primary PCI, the ADIR and ADBR both markedly decreased over time. Although the rates for bleeding exceeded those for ischemia within 30 days, the daily risk of ischemia significantly exceeded the daily risk of bleeding beyond 30 days, supporting the use of intensified platelet inhibition during the first year after STEMI. (J Am Coll Cardiol 2017;70:1846–57) © 2017 by the American College of Cardiology Foundation.

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Patients with ST-segment elevation myocardial infarction (STEMI) who are undergoing primary percutaneous coronary intervention (PCI) are at high risk for ischemic and bleeding events, both of which strongly affect subsequent morbidity and mortality (1–4). The selection of optimal antithrombotic agents in the acute and chronic phases after STEMI, in terms of their potency and duration, requires a careful evaluation of the offsetting risks of ischemia and bleeding (5–7). Although the predictors and impact of ischemic and hemorrhagic events after primary PCI in STEMI have been investigated (1,2), their absolute and relative rates over time remain uncertain. In this regard the risk for recurrent ischemic and bleeding events may not be uniform over time, a consideration that may influence the benefit-to-risk ratio of guideline-recommended antithrombotic therapies. For example, because the highest rate of ischemic events occurs in the first few days or weeks after STEMI (8,9), a strategy of potent platelet inhibition could be considered during the first month after the patient's presentation, if the bleeding risk is not excessive in this period. Thereafter, down-titrating to a less potent regimen could offer a favorable balance of ischemic protection versus bleeding avoidance. Such considerations rely on understanding the relative risks of ischemia and bleeding in different risk periods.

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All adverse outcomes (including recurrent events) must be considered for the true burden of ischemic and bleeding complications to be fully appreciated. However, conventional time-to-event analyses censor patients after the first endpoint event is experienced, thereby masking subsequent recurrent adverse events, reducing statistical power, and diminishing appreciation for the potential benefit (or harm) of preventative therapies (10). We therefore determined the average daily rate (ADR) of all ischemic and bleeding events in the first year after primary PCI in patients enrolled in the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial, to characterize the total and temporal-related burden of adverse outcomes after STEMI.

METHODS

STUDY DESIGN AND OBJECTIVES. The study design of the HORIZONS-AMI trial has been previously described (11,12). Briefly, HORIZONS-AMI was a multicenter, international, open-label, 2×2 factorial randomized controlled trial that enrolled 3,602 patients presenting with STEMI within 12 h from onset of symptoms. Eligible patients were randomized 1:1 to unfractionated heparin (UFH) plus a glycoprotein IIb/IIIa inhibitor (GPI) versus bivalirudin. A total of 3,202 eligible patients were then randomized again in a 3:1 ratio to implantation of either a paclitaxel-eluting stent or a bare metal stent. Aspirin, 324 mg chewed or 500 mg intravenously, was given before PCI, and 75 to 81 mg orally once a day was prescribed indefinitely after discharge. A loading dose of clopidogrel (300 or 600 mg per investigators' discretion) was administered pre-PCI, followed by 75 mg orally once a day for at least 1 year. Clinical follow-up was performed at 30 days, 1 year, 2 years, and 3 years following the index procedure. The study was approved by an Institutional Review Board and/or ethical committee at each center participating in the study. All enrolled patients provided informed written consent.

The objectives of the present study were as follows: 1) to determine the average daily ischemic rate (ADIR) and average daily bleeding rate (ADBR) within different time intervals and overall within the first year following primary PCI for STEMI (the time period for which aspirin and clopidogrel were prescribed for all patients); 2) to examine the extent to which recurrent events contributed to the total burden of adverse outcomes; and 3) to determine whether randomized intraprocedural antithrombotic treatment (bivalirudin monotherapy vs. UFH plus GPI) affected these relative and absolute rates.

ENDPOINT AND TIME INTERVAL DEFINITIONS. ADIR events were defined as cardiac death, myocardial infarction (MI), and definite stent thrombosis (ST). ADBR events were defined as Thrombolysis In Myocardial Infarction (TIMI) major and minor bleeding unrelated to coronary

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ADBR = average daily bleeding rate

ADIR = average daily ischemic rate

ADR = average daily rate

GPI = glycoprotein IIb/IIIa inhibitor

LSMD = least square mean difference

MI = myocardial infarction

PCI = percutaneous coronary intervention

ST = stent thrombosis

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

UFH = unfractionated heparin

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