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Safety of Prasugrel Loading Doses in Patients Pre-Loaded With Clopidogrel in the Setting of Primary Percutaneous Coronary Intervention

Results of a Nonrandomized Observational Study

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ABSTRACT

OBJECTIVES The aim of this study was to assess the safety of the concurrent administration of a clopidogrel and prasugrel loading dose in patients undergoing primary percutaneous coronary intervention.

BACKGROUND Prasugrel is one of the preferred $P2Y_{12}$ platelet receptor antagonists for ST-segment elevation myocardial infarction patients. The use of prasugrel was evaluated clinically in clopidogrel-naive patients.

METHODS Between September 2009 and October 2012, a total of 2,023 STEMI patients were enrolled in the COMFORTABLE (Comparison of Biomatrix Versus Gazelle in ST-Elevation Myocardial Infarction [STEMI]) and the SPUM-ACS (Inflammation and Acute Coronary Syndromes) studies. Patients receiving a prasugrel loading dose were divided into 2 groups: 1) clopidogrel and a subsequent prasugrel loading dose; and 2) a prasugrel loading dose. The primary safety endpoint was Bleeding Academic Research Consortium types 3 to 5 bleeding in hospital at 30 days.

RESULTS Of 2,023 patients undergoing primary percutaneous coronary intervention, 427 (21.1%) received clopidogrel and a subsequent prasugrel loading dose, 447 (22.1%) received a prasugrel loading dose alone, and the remaining received clopidogrel only. At 30 days, the primary safety endpoint was observed in 1.9% of those receiving clopidogrel and a subsequent prasugrel loading dose and 3.4% of those receiving a prasugrel loading dose alone (adjusted hazard ratio [HR]: 0.57; 95% confidence interval [CI]: 0.25 to 1.30, $p = 0.18$). The HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) bleeding score tended to be higher in prasugrel-treated patients ($p = 0.076$). The primary safety endpoint results, however, remained unchanged after adjustment for these differences (clopidogrel and a subsequent prasugrel loading dose vs. prasugrel only; HR: 0.54 [95% CI: 0.23 to 1.27], $p = 0.16$). No differences in the composite of cardiac death, myocardial infarction, or stroke were observed at 30 days (adjusted HR: 0.66, 95% CI: 0.27 to 1.62, $p = 0.36$).

CONCLUSIONS This observational, nonrandomized study of ST-segment elevation myocardial infarction patients suggests that the administration of a loading dose of prasugrel in patients pre-treated with a loading dose of clopidogrel is not associated with an excess of major bleeding events. (Comparison of Biomatrix Versus Gazelle in ST-Elevation Myocardial Infarction [STEMI] [COMFORTABLE]; NCT00962416; and Inflammation and Acute Coronary Syndromes [SPUM-ACS]; NCT01000701). (J Am Coll Cardiol Intv 2015;8:1064–74) © 2015 by the American College of Cardiology Foundation.

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Rapid, potent, and consistent inhibition of platelet aggregation is a cornerstone in the treatment of patients with acute ST-segment elevation myocardial infarction (STEMI) undergoing primary coronary intervention (PCI) to complement optimal epicardial and myocardial reperfusion while protecting against recurrent ischemic events (1). The administration of a clopidogrel loading dose before primary PCI has been shown to reduce ischemic events, with a 600-mg loading dose emerging as the preferred regimen (2,3). Compared with clopidogrel, prasugrel provides a more rapid onset and more potent and consistent inhibition of platelet aggregation (4,5). In STEMI patients undergoing PCI, prasugrel has been shown to be more effective than clopidogrel by reducing the risk of cardiovascular mortality, myocardial infarction, and stroke as well as stent thrombosis (6). Of note, improved efficacy in STEMI patients was not associated with an increased risk of bleeding throughout 15 months of follow-up. Recent guidelines for the management of STEMI patients recommend prasugrel over clopidogrel in patients undergoing primary PCI, without commenting on the use of prasugrel in clopidogrel pre-treated patients (7,8). Clopidogrel, however, is frequently administered upstream, even in STEMI patients. The administration of a prasugrel loading dose in patients already exposed to clopidogrel has raised concerns about bleeding and potential drug interactions, thereby potentially offsetting beneficial effects in terms of efficacy. We therefore assessed the safety and efficacy of 2 loading regimens consisting of clopidogrel and a subsequent prasugrel loading dose and a prasugrel loading dose alone using pre-specified endpoint definitions for safety and efficacy with assessment of adverse events by an independent adjudication committee in a large, contemporary population of STEMI patients undergoing primary PCI. Because no effect of a concomitant loading dose of clopidogrel and prasugrel is expected during the maintenance period of the therapy, the endpoints were assessed at hospital discharge and at 30 days.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

BARC = Bleeding Academic Research Consortium

CI = confidence interval

HR = hazard ratio

IPTW = inverse probability of treatment weighted

PCI = percutaneous coronary intervention

PRU = platelet reactivity unit

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

METHODS

PATIENT POPULATION. Patients with STEMI were considered when participating in the COMFORTABLE (Comparison of Biomatrix Versus Gazelle in ST-Elevation Myocardial Infarction [STEMI]) trial or in the SPUM-ACS (Inflammation and Acute Coronary Syndromes) trial and receiving either a prasugrel loading dose alone or a clopidogrel loading dose and a subsequent prasugrel loading dose. The design of the COMFORTABLE trial has been reported elsewhere (9,10). Briefly, this was a multicenter, randomized, assessor-blinded superiority trial comparing a novel biodegradable polymer-based biolimus-eluting stent with a bare metal stent in STEMI patients undergoing primary PCI. Consecutive patients 18 years of age or

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