JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 7, NO. 10, 2014

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2014.04.020

Impact of Gene Polymorphisms, Platelet Reactivity, and the SYNTAX Score on 1-Year Clinical Outcomes in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

The GEPRESS Study

Tullio Palmerini, MD,* Paolo Calabrò, MD,† Federico Piscione, MD,‡ Stefano De Servi, MD,‖ Marco Cattaneo, MD,¶ Diego Maffeo, MD,# Anna Toso, MD,** Antonio Bartorelli, MD,†† Cataldo Palmieri, MD,‡‡ Marco De Carlo, MD,‖‖ Davide Capodanno, MD,¶¶ Chiara Barozzi, PhD,* Luciana Tomasi, PhD,* Diego Della Riva, MD,* Andrea Mariani, MD,* Nevio Taglieri, MD,* Letizia Bacchi Reggiani, MSc,* Renatomaria Bianchi, MD,† Roberta De Rosa, MD,## Matteo Mariani, MD,‖ GianMarco Podda, MD,¶ Philippe Généreux, MD,*** Gregg W. Stone, MD,*** Dominick J. Angiolillo, MD, PhD†††

ABSTRACT

OBJECTIVES The aim of this study was to investigate the association between high on-treatment platelet reactivity (HPR) and the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score (SS) for risk prediction of major adverse cardiovascular events (MACE) in patients with non–ST-segment elevation acute coronary syndrome (NSTEACS) undergoing percutaneous coronary intervention (PCI).

BACKGROUND Platelet function testing may be used to optimize antiplatelet therapy in high-risk patients, but identification of this category of patients remains challenging.

METHODS The GEPRESS (Gene Polymorphism, Platelet Reactivity, and the Syntax Score) study was a prospective, multicenter, observational study enrolling 1,053 patients with NSTEACS undergoing PCI and treated with clopidogrel. The platelet reactivity index (PRI) was measured at 3 time points: before PCI, at hospital discharge, and 1 month after PCI. Genetic variants of clopidogrel metabolism were determined in 750 patients. Patients were stratified by the presence of HPR (PRI >50%) and by tertile of the SS (upper SS tertile ≥15). The primary objective of this study was the risk of MACE in the period between 1 month and 1 year.

RESULTS Between 1 month and 1 year, 1-month HPR was an independent predictor of MACE in patients with an SS ≥15, but not in those with an SS <15, displaying a 5-fold increase in event rates (10.4% vs. 2.5%; $p < 0.0001$). CYP2C19*2 was the only single nucleotide polymorphism associated with HPR, but it was not associated with MACE. Although there was a significant variability in the PRI across the 1-month period, predischarge HPR and SS effectively stratified the risk of subsequent MACE up to 1-year follow-up.

CONCLUSIONS In clopidogrel-treated patients with NSTEACS undergoing PCI, HPR was independently associated with an increased risk of MACE only in the presence of a high SS. (J Am Coll Cardiol Intv 2014;7:1117–27) © 2014 by the American College of Cardiology Foundation.

From the *Cardiovascular Department, Policlinico S. Orsola, Bologna, Italy; †Department of Cardiothoracic Science, Second University of Naples, A.O. dei Colli, Monaldi, Naples, Italy; ‡Department of Medicine and Surgery, University of Salerno, Salerno, Italy; ‖Legnano Hospital, Legnano, Italy; ¶Department of Health Science, University of Milan, Milan, Italy; #Cardiothoracic Department, Spedali Civili, Brescia, Italy; **Cardiology Division, Prato Hospital, Prato, Italy; ††Monzino Heart Center, IRCCS,

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 7, NO. 10, 2014
OCTOBER 2014:1117–27

ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium

CI = confidence interval

HPR = high on-treatment platelet reactivity

IDI = integrated discrimination improvement

LVEF = left ventricular ejection fraction

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

NSTEACS = non-ST-segment elevation acute coronary syndromes

NSTEMI = non-ST-segment elevation myocardial infarction

OR = odds ratio

PRI = platelet reactivity index

ROC = receiver-operating characteristic

SNP = single nucleotide polymorphism

SS = SYNTAX score

VASP = vasodilator-stimulated phosphoprotein

High on-treatment platelet reactivity (HPR) has emerged as a risk factor for stent thrombosis and major adverse cardiovascular events (MACE) in patients who receive clopidogrel after percutaneous coronary intervention (PCI) (1). Multiple factors can contribute to these pharmacodynamic findings (2). In particular, genetic factors have been shown to be associated with poor responsiveness to clopidogrel (3), but their impact on the risk of MACE is controversial (4,5). Moreover, the low positive predictive value of HPR and the absence of large-scale randomized clinical trials supporting the use of platelet function testing question the utility of routine assessment of platelet reactivity in patients undergoing PCI (6). Accordingly, current guidelines do not endorse routine use of platelet function testing, but they suggest that in selected patients at high risk of a poor outcome after PCI, platelet function testing can be implemented to optimize antiplatelet therapy (7). However, identification of these patients remains challenging.

Prospectively developed for the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial (8), the SYNTAX score (SS) has been shown to be associated with an increased risk of mortality, myocardial infarction (MI), and stent thrombosis in patients with non-ST-segment elevation acute coronary syndromes (NSTEACS) undergoing PCI (9). The relationship between the SS and the presence of HPR for the risk of MACE, however, has never been investigated. Other unsolved dilemmas include the relative prognostic value of platelet function testing versus pharmacogenetic information, the incremental prognostic value of the determination of platelet reactivity over time, and the existence of a therapeutic window for platelet reactivity. On this background, in the present study, we sought to investigate the following: 1) the association between platelet reactivity and the SS for the risk of MACE in patients with NSTEACS undergoing PCI treated with clopidogrel; 2) the association between genetic variants involved in clopidogrel-mediated platelet effects and the risk of MACE; 3) the incremental prognostic value of the platelet reactivity measured at several time points; and 4) the existence of a therapeutic window of platelet reactivity, which could be associated with a low risk of both ischemic and bleeding events.

METHODS

PATIENTS AND STUDY DESIGN. The GEPRESS (Gene Polymorphism, Platelet Reactivity, and the Syntax Score) study is a prospective, multicenter study designed to determine the impact of platelet reactivity, the SS, and the presence of several genetic variants modulating clopidogrel-mediated effects on the risk of ischemic and bleeding events in patients with NSTEACS undergoing PCI and treated with clopidogrel. Patients were eligible for enrollment if they had NSTEACS and at least 1 stenosis >50% requiring PCI. Patients were stratified by the presence of HPR and tertiles of the SS. HPR was defined using the vasodilator-stimulated phosphoprotein (VASP) assay as described in the following. SS was determined by experienced core angiographic laboratory technicians (Cardiovascular Research Foundation, New York, New York) blinded to clinical outcomes. For the purpose of the study, patients in the upper SS tertile (SS ≥15) were compared with patients in the mid or lower tertile (SS <15).

Milan, Italy; ‡‡Department of Interventional Cardiology, Heart Hospital, Massa, Italy; |||Catheterization Laboratory, Azienda Ospedaliero-Universitaria Pisa, Pisa, Italy; ¶¶Ferrarotto Hospital, University of Catania, Catania, Italy; ##Department of Advanced Biomedical Sciences, Università Federico II, Naples, Italy; ***Columbia University Medical Center and the Cardiovascular Research Foundation, New York, New York; and the †††Department of Medicine/Division of Cardiology, University of Florida, Jacksonville, Florida. The study was supported by a research grant from Eli Lilly and Daiichi Sankyo. Dr. Généreux has received speaker's fees from Abbott Vascular. Dr. Stone is consultant for Boston Scientific and Cardiovascular Systems, Inc. Dr. Angiolillo has received consulting fees or honoraria from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Daiichi Sankyo, The Medicines Company, AstraZeneca, Merck, Evolva, Abbott Vascular and PLx Pharma; has participated in review activities for Johnson & Johnson, St. Jude Medical, and Sunovion; and institutional grants from Bristol-Myers Squibb, Sanofi-Aventis, GlaxoSmithKline, Otsuka, Eli Lilly, Daiichi Sankyo, The Medicines Company, AstraZeneca, Evolva, and Gilead; and has received a research grant from Esther and King Biomedical. Dr Capodanno is a member of the Advisory Boards of Eli Lilly, AstraZeneca and The Medicines Company; and a member of the Speaker's bureaus for Eli Lilly and The Medicines Company. Dr. Cattaneo has received speaker honoraria, is on the Advisory Board of, and has received research support from Eli Lilly, Daiichi-Sankyo, and AstraZeneca. Dr. Palmerini has received a research grant from Eli Lilly. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 15, 2014; revised manuscript received April 22, 2014, accepted April 23, 2014.