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Vorapaxar in Acute Coronary Syndrome Patients Undergoing Coronary Artery Bypass Graft Surgery

Subgroup Analysis From the TRACER Trial (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome)

David J. Whellan, MD,* Pierluigi Tricoci, MD, PhD,† Edmond Chen, MD,‡ Zhen Huang, MS,† David Leibowitz, MD,§ Pascal Vranckx, MD,‖ Gregary D. Marhefka, MD,* Claes Held, MD, PhD,¶ Jose C. Nicolau, MD, PhD,# Robert F. Storey, MD, DM,** Witold Ruzyllo, MD,†† Kurt Huber, MD,‡‡ Peter Sinnaeve, MD, PhD,§§ A. Teddy Weiss, MD,§ Jean-Pierre Dery, MD,‖‖ David J. Moliterno, MD,¶¶ Frans Van de Werf, MD,§§ Philip E. Aylward, MD,## Harvey D. White, DSc,*** Paul W. Armstrong, MD,††† Lars Wallentin, MD, PhD,¶ John Strony, MD,‡ Robert A. Harrington, MD,‡‡‡ Kenneth W. Mahaffey, MD‡‡‡

Philadelphia, Pennsylvania; Durham, North Carolina; Whitehouse Station, New Jersey; Jerusalem, Israel; Rotterdam, the Netherlands; Uppsala, Sweden; São Paulo, Brazil; Sheffield, United Kingdom; Warsaw, Poland; Vienna, Austria; Leuven, Belgium; Québec City, Québec and Edmonton, Alberta, Canada; Lexington, Kentucky; Adelaide, Australia; Auckland, New Zealand; and Stanford, California

Objectives This study evaluated effects of protease-activated receptor-1 antagonist vorapaxar (Merck, Whitehouse Station, New Jersey) versus placebo among the TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) study patients with non–ST-segment elevation acute coronary syndromes undergoing coronary artery bypass grafting (CABG).

Background Platelet activation may play a key role in graft occlusion, and antiplatelet therapies may reduce ischemic events, but perioperative bleeding risk remains a major concern. Although the TRACER study did not meet the primary quintuple composite outcome in the overall population with increased bleeding, an efficacy signal with vorapaxar was noted on major ischemic outcomes, and preliminary data suggest an acceptable surgical bleeding profile. We aimed to assess efficacy and safety of vorapaxar among CABG patients.

Methods Associations between treatment and ischemic and bleeding outcomes were assessed using time-to-event analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox hazards model. Event rates were estimated using the Kaplan-Meier method.

Results Among 12,944 patients, 1,312 (10.1%) underwent CABG during index hospitalization, with 78% on the study drug at the time of surgery. Compared with placebo CABG patients, vorapaxar-treated patients had a 45% lower rate of the primary endpoint (i.e., a composite of death, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization during index hospitalization) (HR: 0.55; 95% CI: 0.36 to 0.83; $p = 0.005$), with a significant interaction ($p = 0.012$). The CABG-related Thrombolysis In Myocardial Infarction major bleeding was numerically higher with vorapaxar, but not significantly different between vorapaxar and placebo (9.7% vs. 7.3%; HR: 1.36; 95% CI: 0.92 to 2.02; $p = 0.12$), with no excess in fatal bleeding (0% vs. 0.3%) or need for reoperation (4.7% vs. 4.6%).

Conclusions In non–ST-segment elevation acute coronary syndrome patients undergoing CABG, vorapaxar was associated with a significant reduction in ischemic events and no significant increase in major CABG-related bleeding. These data show promise for protease-activated receptor 1 antagonism in patients undergoing CABG and warrant confirmatory evidence in randomized trials. (Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients With Acute Coronary Syndrome [TRA·CER] [Study P04736AM3]; NCT00527943) (J Am Coll Cardiol 2014;63:1048–57) © 2014 by the American College of Cardiology Foundation

Coronary artery bypass graft (CABG) surgery is the revascularization procedure of choice to treat patients with acute coronary syndromes (ACS) in whom coronary anatomy is not suitable for percutaneous coronary intervention. In CABG patients, subsequent ischemic events may originate in either grafts or in the native coronary artery. Asymptomatic

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graft occlusion occurs in up to 40% of patients within 1 year (symptomatic occlusion occurs in 3.4% of patients) and is associated with a mortality rate of up to 9% (1–3). Graft thrombosis is thought to be the leading mechanism of graft closure, and platelet activation may play a key role in both early and late graft occlusion (4–8). Aspirin improves early vein graft patency and ischemic outcomes, although significant aspirin resistance has been reported after CABG surgery, whereas its effect on long-term patency remains uncertain (9–12). Additional platelet inhibition through the $P2Y_{12}$ receptor with clopidogrel in patients undergoing CABG after ACS was associated with reduced ischemic rates, but concerns regarding operative bleeding risk require preoperative discontinuation and have hindered widespread adoption in the management of ACS patients undergoing CABG (13–18). Consequently, there is a lack of consensus regarding both clopidogrel use post-CABG and opportunities for novel therapeutic agents to fill the treatment gap in non–ST-segment elevation (NSTE) ACS patients undergoing CABG.

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
CABG = coronary artery bypass grafting
CI = confidence interval
CV = cardiovascular
HR = hazard ratio
IQR = interquartile range
MI = myocardial infarction
NSTE = non–ST-segment elevation
PAR = protease-activated receptor
TIMI = Thrombolysis In Myocardial Infarction

Thrombin generation increases during CABG surgery and persists afterward, potentially increasing the risk of thrombotic complications, including graft and native coronary artery thrombosis (19,20). Therefore, the blockade of the main platelet thrombin receptor, the protease-activated receptor (PAR)-1, could be a more specific strategy to reduce graft occlusion and native coronary thrombosis after CABG, thus preventing subsequent ischemic events. Vorapaxar (Merck, Whitehouse Station, New Jersey) is a selective, competitive, oral PAR-1 antagonist

From the *Division of Cardiology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania; †Duke Clinical Research Institute, Durham, North Carolina; ‡Merck Sharp & Dohme Corp., Whitehouse Station, New Jersey; §Heart Institute, Hadassah–Hebrew University Medical Center, Jerusalem, Israel; ||Thoraxcentre, Rotterdam, the Netherlands; ¶Department of Medical Sciences, Uppsala Clinical Research Center, Uppsala, Sweden; #Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil; **Department of Cardiovascular Science, University of Sheffield, Sheffield, United Kingdom; ††Department of Coronary Artery Disease and Cardiac Catheterization Laboratory, Institute of Cardiology, Warsaw, Poland; ‡‡3rd Department of Medicine, Cardiology and Emergency Medicine, Wilhelminen Hospital, Vienna, Austria; §§Department of Cardiology, University of Leuven, Leuven, Belgium; ||||Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec City, Québec, Canada; ¶¶Gill Heart Institute and Division of Cardiovascular Medicine, University of Kentucky, Lexington, Kentucky; ##South Australian Health and Medical Research Institute, Flinders University and Medical Centre, Adelaide, Australia; ***Green Lane Cardiovascular Service, Auckland City Hospital, Auckland, New Zealand; †††Division of Cardiology, University of Alberta, Edmonton, Alberta, Canada; and the ‡‡‡Department of Medicine, Stanford University, Stanford, California. 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Dr. Harrington's disclosures are listed at: http://med.stanford.edu/profiles/medicine/frdActionServlet?choiceId=showCOIs&&fid=34240. Dr. Mahaffey's full disclosures prior to August 1, 2013 are available at www.dcri.org; disclosures after August 1, 2013 are available at: http://med.stanford.edu/profiles/kenneth_mahaffey. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Dr. Chen is currently affiliated with Global Clinical Development, Bayer HealthCare Pharmaceuticals Inc., Whippany, New Jersey.

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