Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 11, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.10.048

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

See page 1058

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. The TRACER trial was funded by Merck & Co., Inc. Dr. Whellan has received consultant honoraria from Novartis, POZEN, Terumo, and Medtronic; and he has received a research grant from Merck & Co., Inc., and Medtronic. Dr. Tricoci has received a consultant agreement and research grant from Merck & Co., Inc. Dr. Chen was an employee of Merck & Co., Inc. Dr. Held has received research support from Merck & Co., Inc., GlaxoSmithKline, AstraZeneca, and Bristol-Myers Squibb/Pfizer; has received institutional research grants from Schering-Plough/Merck Sharp & Dohme and Roche; has served on the advisory board for Pfizer and AstraZeneca; and has received lecture fees from AstraZeneca. Dr. Nicolau has received research grant support and consulting fees/honorarium from Merck & Co., Inc.; has board membership with AstraZeneca; has received research grant support and lecture fees, including service on speakers' bureaus from AstraZeneca and Eli Lilly; and has received travel/accommodations/meeting expenses from AstraZeneca. Dr. Storey has received research grants from AstraZeneca, Eli Lilly/Daiichi Sankyo Alliance, Merck & Co., Inc., and Accumetrics; has served as a consultant for AstraZeneca, Eli Lilly, Daiichi Sankyo, Novartis, Merck & Co., Inc., Eisai, Sanofi-Aventis/Regeneron, Bristol-Myers Squibb, Roche, and Accumetrics; and has received honorarium from AstraZeneca, Eli Lilly, Daiichi Sankyo, Merck & Co., Inc., Accumetrics, Medscape, and Iroko. Dr. Ruzyllo has received honoraria for lectures and clinical studies from Bayer, Bristol-Myers Squibb/Pfizer, Merck & Co., Inc., Daiichi Sankyo, Eli Lilly, and Sanofi-Aventis. Dr. Huber has received honoraria for lectures and expert rounds from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, Eli Lilly, Sanofi-Aventis, and The Medicines Company. Dr. Sinnaeve has received a research grant from AstraZeneca; has received advisory/speakers fees from Merck Sharp & Dohme, Merck & Co., Inc., Sanofi-Aventis, Bristol-Myers Squibb, Eli Lilly, Daiichi Sankyo, AstraZeneca, Boehringer Ingelheim, Pfizer, and Bayer; and has served on the advisory board of Merck Sharp & Dohme. Dr. Moliterno has received research support and consulting fees/honoraria from Merck & Co., Inc. Dr. Van de Werf has received a research grant from Merck Sharp & Dohme; has received research support from Merck & Co., Inc. and Boehringer Ingelheim; and has served as a consultant for and received lecture fees from AstraZeneca and Boehringer Ingelheim. Dr. Aylward has received research support from Merck & Co., Inc., AstraZeneca, Eli Lilly, and Bayer/Johnson & Johnson; has served as a consultant for AstraZeneca, Boehringer Ingelheim, Pfizer, Sanofi-Aventis, and Eli Lilly; and has received lecture fees from AstraZeneca, Boehringer Ingelheim, and Eli Lilly. Dr. White has received research support from Sanofi-Aventis, Eli Lilly, The Medicines Company, National Institutes of Health, Pfizer, Roche, Johnson & Johnson, Merck Sharpe & Dohme, AstraZeneca, GlaxoSmithKline, Daiichi Sankyo Pharma Development, and Bristol-Myers Squibb; and has served on advisory boards for Merck Sharpe & Dohme, and Regado Biosciences. Dr. Armstrong has received research support and consulting fees/honoraria from Merck Sharp & Dohme; has served as a consultant for Eli Lilly, Regado Biosciences, F. Hoffmann-La Roche Ltd., GlaxoSmithKline, Sanofi-Aventis, Takeda Pharmaceuticals, and Merck & Co., Inc.; has received a research grant from Schering-Plough Research Institute; and has received research support from Boehringer Ingelheim, Sanofi-Aventis Canada, GlaxoSmithKline, AstraZeneca, Regado Biosciences, Amylin, and Novartis. Dr. Wallentin has received research support and consulting fees/honoraria from Merck & Co., Inc.; has performed consultancy for Regado Biotechnologies, Portola, C.S.L. Behring, Athera Biotechnologies, Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline, Bristol-Myers Squibb, and Pfizer; has received research support and lecture fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, GlaxoSmithKline, and Schering-Plough; has received honoraria from Boehringer Ingelheim; and has received honoraria and travel support from AstraZeneca, Bristol-Myers Squibb, and Pfizer. Dr. Strony is an employee and stockholder of Merck & Co., Inc. 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.

Manuscript received May 1, 2013; accepted October 1, 2013.

that inhibits thrombin-mediated platelet activation (21). In addition, in animal models, vorapaxar analogues did not increase surgical bleeding (22). In the TRACER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) trial, among patients with NSTE ACS, vorapaxar did not significantly reduce a quintuple endpoint of cardiovascular (CV) death, myocardial infarction (MI), stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization, but it was associated with a reduction in the composite of CV death, MI, and stroke, largely due to a reduction of MI (23). Similarly, in a study of patients with chronic atherosclerotic disease, the rates of death, MI, and stroke were significantly reduced by vorapaxar (24). In both trials, vorapaxar was associated with a significant increase in major bleeding. We undertook a pre-specified analysis to assess the efficacy and safety of vorapaxar in TRACER patients undergoing CABG.

Methods

The analysis population includes patients who were randomized in the TRACER trial (n = 12,944), for which the primary results and study design have been published (23,25). Briefly, patients were enrolled if they presented with acute symptoms of coronary ischemia within 24 h before hospital presentation and with at least 1 of the following: cardiac troponin (I or T) or creatine kinase-myocardial band levels higher than the upper limit of normal, new ST-segment depression >0.1 mV, or transient ST-segment elevation (<30 min) of >0.1 mV in ≥2 contiguous leads. Patients were randomly assigned in a 1:1 ratio to receive vorapaxar (40-mg loading dose and 2.5-mg daily maintenance dose thereafter) or matching placebo with stratification according to intention to use a glycoprotein IIb/IIIa inhibitor (vs. none) and intention to use a parenteral direct thrombin inhibitor (vs. other antithrombins).

This analysis included patients who underwent CABG during index hospitalization after they were randomized and began the study drug. Because time to CABG may vary across centers, and because it may be local practice to discharge patients and then schedule CABG, we performed an additional analysis to include all CABG surgeries performed within 30 days of randomization.

The study protocol recommended that the study drug be continued during CABG. Temporary interruptions were defined as any disruption in study drug ≥2 days, but then resumed. Permanent discontinuation was definitive premature interruption of study treatment. For the efficacy endpoints, the accrual period was from CABG to the date of site notification of study termination. The endpoints for this analysis were: 1) the composite of CV death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization (primary); and 2) the composite of CV death, MI, or stroke (secondary) from the TRACER study.

For bleeding endpoints, the accrual period was from CABG to the last dose of randomized treatment. The CABG-related major bleeding was defined according to the Thrombolysis In Myocardial Infarction (TIMI) criteria and was pre-specified as part of the TRACER trial event definition. To provide further detail, CABG-related major bleeding was defined as any hemorrhage meeting any of the following criteria: 1) fatal bleeding (i.e., bleeding that directly results in death); 2) perioperative intracranial bleeding; 3) reoperation after closure of the sternotomy incision to control bleeding; 4) transfusion of ≥5 U of whole blood or packed red blood cells within 48 h; or 5) chest tube output >2 l within 24 h. All efficacy and bleeding events in the TRACER study were systematically adjudicated by a central clinical events committee. All bleeding events were classified according to the TIMI and GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) scales.

Associations between treatment assignments and outcomes were assessed using time-to-event analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression modeling, with the adjustment of randomization stratification factors and baseline covariates. Event rates were estimated by the Kaplan-Meier method. To test interaction, because patients had to be classified as either "CABG" or "no CABG" within a common time point (discharge from the index event), the event accrual period was from discharge to site notification. A sensitivity analysis was also carried out by including all events since randomization and accounting for propensity of having CABG.

The SAS version 9.3 (SAS Institute, Cary, North Carolina) was used to perform statistical analyses. The p values were not adjusted for multiple comparisons. The TRACER study was approved by an institutional review committee, and all patients gave informed consent.

Results

Baseline characteristics. In total, 1,312 (10.1%) of 12,944 patients enrolled in the TRACER trial underwent CABG surgery during the index hospitalization (vorapaxar n = 639; placebo n = 673). There were 1,510 patients who underwent CABG within 30 days of randomization (vorapaxar n = 750; placebo n = 760). The overall study population was followed for a median of 502 days (interquartile range [IQR]: 349 to 667 days). The 2 treatments arms were well balanced regarding baseline characteristics for patients undergoing CABG (Table 1).

Study treatment and concomitant antiplatelet agents. The median time to CABG in patients treated with vorapaxar was 120 h (IQR: 47 to 194 h) and with placebo was 119 h (IQR: 48 to 214 h) (Table 2). At randomization, there was a lower utilization of thienopyridine in patients later undergoing CABG (72% CABG vs. 89% no CABG), although use was similar between the vorapaxar and placebo groups. Before CABG, the study drug was interrupted in 23% of placebo patients and in 26% of vorapaxar patients. Among those who had the treatment withheld before

Table 1 Baseline Characteristics of Patients With and Without CABG During Index Hospitalization by Treatment Arm

Characteristic	CABG		No CABG	
	Placebo (n = 673)	Vorapaxar (n = 639)	Placebo (n = 5,798)	Vorapaxar (n = 5,834)
Age (yrs)	64 (58–71)	64 (58–71)	64 (57–72)	64 (58–71)
≥75	89 (13.2)	95 (14.9)	1,007 (17.4)	1,015 (17.4)
Female	155 (23.0)	132 (20.7)	1,667 (28.8)	1,678 (28.8)
Race or ethnic group*				
White	568 (84.7)	548 (85.8)	4,940 (85.4)	4,981 (85.6)
Black	16 (2.4)	17 (2.7)	145 (2.5)	134 (2.3)
Asian	37 (5.5)	32 (4.9)	496 (8.6)	491 (8.4)
Other	48 (7.2)	42 (6.6)	201 (3.5)	211 (3.6)
Body mass index (kg/m^2)	28.1 (25.4–31.4)	28.2 (25.2–31.7)	27.7 (25.0–31.1)	27.7 (25.0–31.1)
Region of enrollment				
North America	242 (36.0)	243 (38.0)	1,452 (25.0)	1,467 (25.2)
Latin America	83 (12.3)	59 (9.2)	337 (5.8)	369 (6.3)
Western Europe	253 (37.6)	231 (36.2)	2,677 (46.2)	2,678 (45.9)
Eastern Europe	50 (7.4)	58 (9.1)	692 (11.9)	687 (11.8)
Asia	25 (3.7)	21 (3.3)	449 (7.7)	441 (7.6)
Australia or New Zealand	20 (3.0)	27 (4.2)	191 (3.3)	192 (3.3)
Cardiovascular risk factors				
Hypertension	482 (71.6)	482 (75.4)	4,109 (70.9)	4,055 (69.5)
Hyperlipidemia	418 (62.1)	417 (65.3)	3,606 (62.2)	3,621 (62.1)
Diabetes mellitus	237 (35.2)	220 (34.4)	1,793 (30.9)	1,820 (31.2)
Current tobacco use	176 (26.2)	182 (28.5)	1,611 (27.8)	1,567 (26.9)
Creatinine clearance				
<30 ml/min	7 (1.1)	9 (1.5)	81 (1.5)	93 (1.7)
30–60 ml/min	62 (9.7)	59 (9.7)	681 (12.4)	675 (12.2)
Cardiovascular disease history				
MI	143 (21.3)	170 (26.6)	1,747 (30.1)	1,731 (29.7)
PCI	99 (14.7)	127 (19.9)	1,432 (24.7)	1,432 (24.6)
CABG	20 (3.0)	23 (3.6)	746 (12.9)	754 (12.9)
Stroke	28 (4.2)	21 (3.3)	234 (4.0)	270 (4.6)
PAD	46 (6.8)	52 (8.2)	422 (7.3)	416 (7.1)
Positive for troponin or CK-MB	627 (93.6)	602 (94.2)	5,410 (93.9)	5,411 (93.5)
ECG findings				
ST-segment depression	257 (38.2)	252 (39.4)	1,865 (32.2)	1,825 (31.3)
ST-segment elevation†	36 (5.4)	29 (4.5)	342 (5.9)	329 (5.4)
Killip class‡				
II	32 (4.8)	34 (5.4)	228 (4.0)	200 (3.5)
III or IV	6 (0.90)	6 (0.94)	55 (0.96)	63 (1.1)
Use of oral antiplatelets at baseline				
Thienopyridine	488 (72.1)	452 (70.7)	5,151 (88.8)	5,216 (89.4)
Aspirin				
≤100 mg	373 (58.7)	340 (55.7)	3,405 (60.4)	3,405 (60.5)
>100 mg	263 (41.4)	271 (44.4)	2,231 (39.6)	2,227 (39.5)

Values are median (interquartile range) or n (%). *Race or ethnic group was reported by investigators after interviews with patients. †Patients with transient (<30 min) ST-segment elevation were eligible. ‡According to the Killip classification, class II indicates cardiac S3 or rales on ≤50% of the lung fields, class III indicates rales on >50% of the lung fields, and class IV indicates signs of cardiogenic shock.

CABG = coronary artery bypass grafting; CK-MB = creatine kinase-myocardial band; ECG = electrocardiogram; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention.

surgery, the median time from last dose to CABG was 6 days (IQR: 4 to 8 days) for placebo and vorapaxar patients.

In those who underwent CABG, 39% in the placebo group and 38% in the vorapaxar group received clopidogrel within 5 days of CABG. Clopidogrel at discharge was used in 16% of placebo patients and in 19% of vorapaxar patients, which was much lower than among non-CABG patients (84.3% placebo; 84.9% vorapaxar).

Efficacy of vorapaxar in CABG patients. In patients undergoing CABG during index hospitalization (n = 1,312),

Table 2 Peri-CABG Antiplatelet Therapies

	Placebo (n = 673)	Vorapaxar (n = 639)
Study drug loading dose to CABG (h)	119 (48–214)	120 (47–194)
Study drug interrupted	155 (23)	166 (26)
Time from last study drug dose after interruption (days)	6 (4–8)	6 (4–8)
Clopidogrel received ≤5 days from CABG	263 (39)	242 (38)
Clopidogrel at discharge	108 (16)	121 (19)

Values are median (interquartile range) or n (%).
CABG = coronary artery bypass grafting.

the primary endpoint occurred in 43 patients in the vorapaxar group and in 70 patients in the placebo group (2-year Kaplan-Meier rates: 8.2% and 12.9%, respectively), corresponding to a 45% reduction (adjusted HR: 0.55; 95% CI: 0.36 to 0.83; p = 0.005) (Table 3). The reduction in events post-discharge was higher among patients who underwent CABG during index hospitalization (HR: 0.46; 95% CI: 0.28 to 0.77; p = 0.003) compared with those who did not undergo CABG during index hospitalization (HR: 0.97; 95% CI: 0.87 to 1.08; p = 0.59). There was a statistically significant interaction between CABG and vorapaxar (p = 0.012) (Fig. 1). All components of the primary endpoint were numerically lower with vorapaxar. When all patients who underwent CABG in the first 30 days after randomization were included, the effect on post-CABG events remained consistent, with a 48% reduction with vorapaxar (HR: 0.52; 95% CI: 0.36 to 0.76; p = 0.001), and the interaction between CABG and vorapaxar treatment effect on post-discharge events remained significant with groups defined at 30 days (p = 0.028).

Vorapaxar was also associated with lower occurrence of the key secondary endpoint (43 events; 2-year Kaplan-Meier rate of 8.2%) compared with placebo (58 events; 2-year Kaplan-Meier rate of 10.2%) in patients undergoing CABG (adjusted HR: 0.66; 95% CI: 0.43 to 1.01; p = 0.057). The reduction in post-discharge events was numerically higher among patients who underwent CABG (HR: 0.54; 95% CI: 0.31 to 0.94; p = 0.030) compared with those who did not undergo CABG (HR: 0.89; 95% CI: 0.78 to 1.01; p = 0.065). The interaction between randomized treatment and CABG was not statistically significant (p = 0.209) (Fig. 2). Results were comparable when all patients who underwent CABG in the first 30 days post-randomization were included (HR: 0.60; 95% CI: 0.40 to 0.88; p = 0.010).

CABG-related bleeding. The CABG-related TIMI major bleeding was not a statistically significant difference between vorapaxar and placebo, although it was numerically higher with vorapaxar (HR: 1.36; 95% CI: 0.92 to 2.02; p = 0.12), as it was for GUSTO severe bleeding related to CABG (HR: 1.35; 95% CI: 0.80 to 2.29; p = 0.26) (Table 4). The number of patients who required repeated surgery to control bleeding was similar between groups (vorapaxar n = 30 [4.7%]; placebo n = 31 [4.6%]). Fatal bleeding occurred in 2 placebo patients and in none of the vorapaxar patients. Among those who continued the study drug up to the time of surgery, TIMI major CABG-related bleeding occurred in 43 (8.0%) placebo patients and in 54 (11.0%) vorapaxar patients.

Among those who discontinued the randomized drug throughout CABG, TIMI major CABG-related bleeding occurred in 9 (7.3%) placebo patients and in 13 (9.3%) vorapaxar patients. Reoperation for bleeding in this subgroup was similar between the vorapaxar (n = 7 [5.0%]) and placebo (n = 7 [5.6%]) groups, and in the group of patients who continued the drug through the perioperative period (vorapaxar: n = 23 [4.6%]; placebo: n = 24 [4.4%]). In patients

Table 3 Primary and Key Secondary Efficacy Endpoints Post-CABG Among Patients Who Underwent CABG During Index Hospitalization and Within 30 Days of Randomization

	Placebo (2-yr Kaplan-Meier Rate)	Vorapaxar (2-yr Kaplan-Meier Rate)	HR* (95% CI)	p Value
CABG during index hospitalization	n = 673	n = 639	—	—
Primary endpoint	70 (12.9%)	43 (8.2%)	0.55 (0.36–0.83)	0.005
CV death	26	14	—	—
MI	26	21	—	—
Stroke	17	14	—	—
Urgent revascularization	10	5	—	—
Recurrent ischemia with hospitalization	6	2	—	—
Key secondary endpoint†	58 (10.2%)	43 (8.2%)	0.66 (0.43–1.01)	0.057
CABG within 30 days	n = 760	n = 750	—	—
Primary endpoint‡	83 (13.5%)	49 (8.1%)	0.52 (0.36–0.76)	0.001
Key secondary endpoint†	70 (8.6%)	48 (6.7%)	0.60 (0.40–0.88)	0.010

Values are n (%) or %. Interaction of index CABG and vorapaxar: primary endpoint adjusted p = 0.012; key secondary endpoint adjusted p = 0.21. Interaction of CABG within 30 days and vorapaxar: primary endpoint adjusted p = 0.028; key secondary endpoint adjusted p = 0.24. The number of events is from CABG to site notification. Kaplan-Meier rates reported are 2-year estimates. HRs for comparisons between vorapaxar and placebo in patients undergoing CABG during index hospitalization were adjusted for randomization stratification factors and baseline covariates. *Reference group is placebo arm, adjusted for baseline covariates. †Cardiovascular death, myocardial infarction, and stroke. ‡Cardiovascular death, myocardial infarction, stroke, urgent revascularization, and recurrent ischemia with rehospitalization.
CABG = coronary artery bypass grafting; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction.

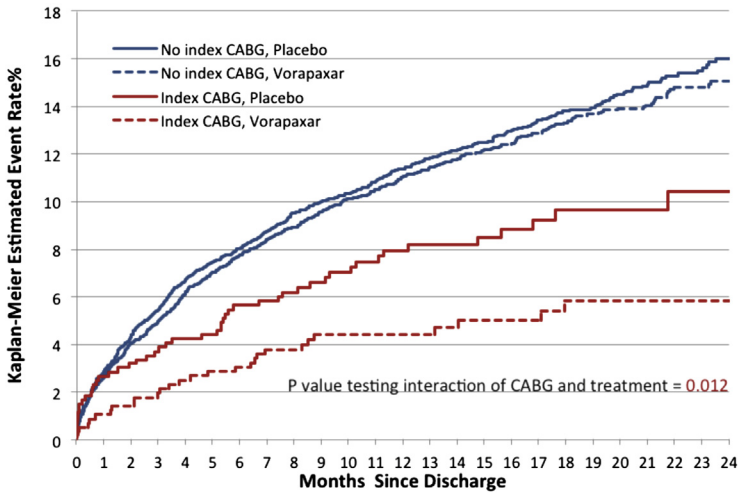

Figure 1 Primary Efficacy Endpoint by Index CABG and Treatment Post-Discharge From Index Hospitalization

CABG = coronary artery bypass grafting.

who received clopidogrel within 5 days of surgery (vorapaxar n = 242; placebo n = 263), TIMI major CABG-related bleeding occurred in 28 (11.6%) patients with vorapaxar and in 23 (8.7%) patients with placebo, and reoperation for bleeding occurred in 10 (4.1%) patients with vorapaxar and 13 (4.9%) patients with placebo. Among patients who received their last dose of clopidogrel ≥5 days before CABG (vorapaxar n = 214; placebo n = 231), TIMI major CABG-related bleeding occurred in 26 (12.1%) patients with vorapaxar and in 17 (7.4%) patients with placebo, and reoperation for bleeding occurred in 11 (5.1%) patients with vorapaxar and in 12 (5.2%) patients with placebo.

There was a mild excess in chest tube drainage in patients treated with vorapaxar versus placebo at 8 h (350 ml vs. 308 ml), at 24 h (635 ml vs. 580 ml), and total (830 ml vs. 780 ml).

When all CABG surgeries performed during the first 30 days from randomization were included, the results for CABG-related major bleeding were similar (Table 4).

Bleeding after discharge. In patients who underwent CABG during index hospitalization, bleeding after discharge increased with vorapaxar (Table 5). In the CABG population, GUSTO moderate or severe bleeding at 2 years was 4.0% with vorapaxar and 2.2% with placebo (HR: 1.60; 95% CI: 0.75 to 3.42). The TIMI major bleeding was infrequent in the CABG cohort, but increased with vorapaxar (2-year Kaplan-Meier rates of 1.4% with vorapaxar and 0.8% with placebo; HR: 1.83; 95% CI: 0.54 to 6.26). In the CABG cohort, there was 1 patient (0.2%) with intracranial hemorrhage who received vorapaxar and no intracranial hemorrhage with placebo. In the non-CABG population, the GUSTO moderate or severe bleeding rate at 2 years was 4.1% with vorapaxar and 2.8% with placebo (HR: 1.38; 95% CI: 1.09 to 1.75). There was no statistically significant interaction (p = 0.75).

Discussion

In the TRACER study patients who underwent CABG, we observed that adding vorapaxar versus placebo to standard-of-care practices reduced the occurrence of the primary endpoint with an estimated relative hazard reduction of 45%. The improvement in the primary endpoint post-discharge for patients randomized to vorapaxar and undergoing CABG during index hospitalization appeared to be much stronger than that observed in the non-CABG cohort, a finding supported by a statistically significant interaction. In the CABG cohort, vorapaxar was also associated with a 34% reduction of CV death, MI, or stroke (a larger estimated effect than in the main TRACER study cohort), although the interaction was not statistically significant. There was a nonsignificant numerical increase in surgical bleeding with vorapaxar without increased occurrence of reoperations for bleeding. There was also an increase in non-CABG bleeding, which is consistent with the main results of the TRACER trial.

These results suggest that PAR-1 antagonism may be a viable therapeutic option to reduce recurrent ischemic events post-CABG. All components of the primary endpoint, including mortality, were numerically lower with vorapaxar after CABG, and the efficacy of vorapaxar seemed overall enhanced post-CABG. It is possible that PAR-1 activation is an important mechanism leading to graft failure. Particularly, increased thrombin generation after CABG may induce a higher susceptibility to the action of PAR-1 antagonists (26,27). Concomitant

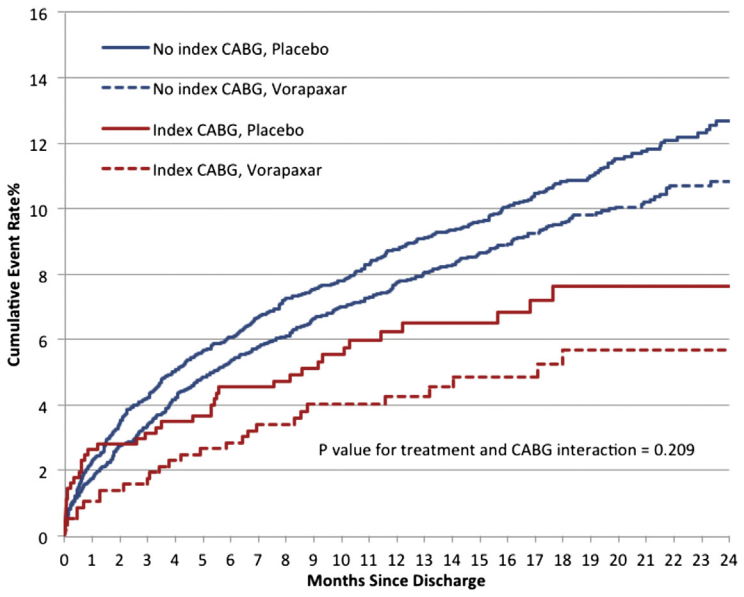

Figure 2 Key Secondary Endpoint by Index CABG and Treatment Post-Discharge From Index Hospitalization

CABG = coronary artery bypass grafting.

antiplatelet therapy might have also played a role. In fact, consistent with registry data, use of clopidogrel at discharge was much lower in CABG patients than in non-CABG patients (18% vs. 85%, respectively). It is possible that the effect of vorapaxar is stronger when added to aspirin only versus when added to aspirin and clopidogrel as triple oral antiplatelet therapy. It is interesting that vorapaxar was associated with a numerical reduction of urgent revascularization (not associated with an MI) in CABG patients, but not in non-CABG patients. Vorapaxar may affect the mechanism leading to urgent revascularization in CABG patients (e.g., graft failure), but not in non-CABG patients

Table 4 CABG-Related Bleeding Among Patients Who Underwent CABG During Index Hospitalization or Within 30 Days of Randomization

Endpoint	Placebo	Vorapaxar	OR* (95% CI)	p Value
CABG during index hospitalization	n = 671	n = 639	—	—
TIMI major	49 (7.3)	62 (9.7)	1.36 (0.92–2.02)	0.12
GUSTO severe	26 (3.9)	33 (5.2)	1.35 (0.80–2.29)	0.26
GUSTO moderate/severe	101 (15.1)	116 (18.2)	1.25 (0.93–1.68)	0.13
Fatal bleeding	2 (0.3)	0 (0.0)	—	—
Reoperation for bleeding	31 (4.6)	30 (4.7)	—	—
Chest tube drainage, ml				
8 h	308 (200–510)	350 (220–550)	—	—
24 h	580 (389–865)	635 (420–1,000)	—	—
Total	780 (490–1,260)	830 (530–1,381)	—	—
CABG within 30 days	n = 758	n = 750	—	—
TIMI major	56 (7.4)	66 (8.8)	1.21 (0.83–1.75)	0.32
GUSTO severe	29 (3.8)	37 (4.9)	1.30 (0.79–2.10)	0.29
GUSTO moderate/severe	111 (14.6)	126 (16.8)	1.18 (0.89–1.55)	0.25
Fatal bleeding	2 (0.3)	0 (0.0)	—	—
Chest tube drainage, ml				
8 h	310 (200–500)	350 (220–550)	—	—
24 h	600 (400–875)	650 (420–995)	—	—
Total	800 (500–1,270)	830 (530–1,370)	—	—

Values are n (%) or median (interquartile range). *Reference group is placebo arm, adjusted for baseline covariates.

GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries; OR = odds ratio; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 3.

Table 5 Bleeding Endpoints Post-Discharge Among Patients Who Underwent CABG During Index Hospitalization and/or Within 30 Days of Randomization

Endpoint	Placebo (2-yr Kaplan-Meier rate)	Vorapaxar (2-yr Kaplan-Meier rate)	HR* (95% CI)	p Value
CABG during index hospitalization	n = 671	n = 639		
GUSTO criteria				
Moderate or severe bleeding	11 (2.2)	17 (4.0)	1.60 (0.75–3.42)	0.225
Severe bleeding	2 (0.3)	7 (1.4)	3.64 (0.76–17.53)	0.107
TIMI criteria				
Clinically significant bleeding	23 (6.0)	48 (11.2)	2.16 (1.31–3.56)	0.002
Major bleeding	4 (0.8)	7 (1.4)	1.83 (0.54–6.26)	0.334
Major or minor bleeding	6 (1.1)	15 (3.7)	2.59 (1.01–6.68)	0.049
Intracranial hemorrhage	0 (0.0)	1 (0.2)	—	—
CABG within 30 days	n = 758	n = 750		
GUSTO criteria				
Moderate or severe bleeding	10 (2.0)	16 (3.3)	1.65 (0.74–3.64)	0.219
Severe bleeding	0 (0.0)	9 (1.6)	—	—
TIMI criteria				
Clinically significant bleeding	27 (6.3)	49 (9.9)	1.83 (1.14–2.93)	0.012
Major bleeding	2 (0.4)	7 (1.2)	3.75 (0.78–18.14)	0.100
Major or minor bleeding	5 (0.9)	14 (3.0)	2.83 (1.02–7.86)	0.046
Intracranial hemorrhage	0 (0.0)	2 (0.4)	—	—

Values are n (%). *Reference group is placebo arm, adjusted for baseline covariates.
Abbreviations as in Tables 3 and 4.

(e.g., in-stent restenosis, progression of pre-existing stenosis).

The use of antiplatelet therapy in addition to aspirin therapy is controversial due to the increased risk of bleeding that undermines the reduction in clinical events. In the CURE (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events) trial (14), the reduction of CV death, MI, or stroke in the CABG cohort was consistent with the main CURE trial results. However, available evidence is controversial concerning a benefit in adding clopidogrel post-CABG to improve vein graft patency and CV events (28–30). Ticagrelor, a reversibly binding, direct-acting oral $P2Y_{12}$ receptor antagonist, was associated with a 16% reduction in CV death, MI, or stroke, which was consistent overall with the main trial results, although ticagrelor appeared to have a more robust effect on mortality in the CABG cohort (15,16). The CABG bleeding rates were increased and comparable for both ticagrelor and clopidogrel (15,18). Based on these results, guidelines recommend withholding either ticagrelor or clopidogrel 5 days prior to CABG surgery (31). A third $P2Y_{12}$ antagonist, prasugrel (vs. clopidogrel), was associated with significantly reduced mortality after adjusting for pre-operative risk in the few patients participating in the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) trial who underwent follow-up CABG surgery (32). However, prasugrel requires an even longer interruption (7 days) before surgery, and the improved clinical outcomes with prasugrel need to be weighed against the substantial increased risk of CABG-related bleeding. In contrast, vorapaxar (or matching placebo) was to be continued perioperatively, as recommended by the TRACER study protocol.

In contrast with the main TRACER study results, in which there was a significant increase in major bleeding with vorapaxar, the perioperative safety profile of vorapaxar seemed acceptable in this analysis. In patients who received vorapaxar, there was a numerical increase in major CABG-related bleeding that did not meet statistical significance, a modest increase in chest tube drainage, and no trend indicating increased rates of reoperation to control bleeding. It is important to note that most CABG procedures were performed while vorapaxar was still active, unlike current recommendations for $P2Y_{12}$ antagonists. In fact, 75% of patients in the vorapaxar group did not have interruption in study treatment before CABG. In addition, because the effect of duration of a single dose of vorapaxar is 2 to 3 weeks and the median time to CABG was only 120 h, even when the study drug was interrupted, it was still expected to be within its biological activity time frame. Our results confirm: 1) earlier findings that show no increase in surgical bleeding in an animal model with a vorapaxar analogue; and 2) preliminary results among 76 patients undergoing CABG in the phase II study, in which vorapaxar did not increase surgical bleeding (33). Overall, these data suggest the possibility of using vorapaxar during the perioperative period. The contrast between surgical and spontaneous bleeding effects of vorapaxar observed in this analysis could be related to different roles of PARs under different pathophysiologic circumstances.

It is possible that, during surgery, a high concentration of thrombin can increase activity of the PAR-4 receptor—which, in humans, requires higher concentrations

JACC Vol. 63, No. 11, 2014
March 25, 2014:1048–57

of thrombin to be activated than PAR-1 does—therefore creating a "rescue" mechanism (34). Alternatively, thrombin generation during cardiopulmonary bypass surgery may cause platelet activation that leads to the desensitization of platelets and a reduction of platelet reactivity. By reducing perioperative, thrombin-mediated platelet activation, vorapaxar may prevent desensitization of platelets. Finally, it is possible that the PAR-1 receptor may have a more limited role in normal hemostasis after major vessel injury (35). Future analysis to also assess the safety of vorapaxar in the setting of noncardiac surgery will be helpful to further define how PAR-1 antagonism could be tolerated in the setting of surgical procedures.

The effect of vorapaxar on bleeding events (mostly representing spontaneous bleeding) after discharge in CABG patients is largely consistent with the overall TRACER study results, particularly in terms of a relative increase in bleeding. However, it is noteworthy that the absolute risk of bleeding is lower in CABG patients than in non-CABG patients, possibly due to the selection of candidates who undergo surgery and the lower concomitant use of clopidogrel. Therefore, the trade-off between efficacy and bleeding may be favorable to vorapaxar use in CABG patients, if the results of the present analysis are confirmed in a prospective randomized clinical trial.

Study limitations. Because the current analysis is not a randomized comparison of vorapaxar and placebo, the results have no immediate applicability in clinical practice and should be interpreted as hypothesis-generating. This is a pre-specified analysis of a post-randomization subgroup within a large clinical trial. Thus, we cannot rule out that study participation and study drug assignment may have influenced the choice of candidates for CABG, or that factors other than CABG itself may have influenced the results. It is important to note, however, that this was a double-blinded study and the time to CABG was short, so it is unlikely that there is bias of CABG referral based on treatment assignment. The vorapaxar and placebo groups were well balanced in the CABG and the non-CABG cohorts regarding baseline demographics. However, unmeasured confounders cannot be excluded with certainty.

Because the primary focus of the TRACER trial was not the evaluation of vorapaxar in patients undergoing CABG, data that may have improved our understanding of the underlying mechanism supporting these results—including the reason for patient referral to CABG, method for harvesting vein grafts, use of cardiopulmonary bypass circuit, or post-operative imaging of vein grafts—were not collected as part of the analysis (36,37). In particular, we did not collect imaging to assess graft failure; therefore, we are unable to provide a mechanistic explanation in support of the observed effect.

The CABG group represents 10% of the overall study population, and the study was not stratified by CABG. Some of the results and lack of statistical significance may have been influenced by insufficient power. No adjustment for multiple comparisons was performed so as not to reduce sensitivity in generating hypotheses.

Conclusions

In a large, nonrandomized cohort of patients with NSTE ACS who participated in the TRACER trial and subsequently underwent CABG, we have observed a marked reduction in the primary endpoint among patients assigned to vorapaxar and enhanced efficacy in comparison with the non-CABG cohort. The current analysis suggests that vorapaxar may have an acceptable safety profile for CABG-related bleeding. After discharge, rates of major bleeding were relatively low in CABG patients, but were increased with vorapaxar, consistent with the main trial. These results should be considered exploratory, yet they suggest that PAR-1 antagonism could be a potentially attractive strategy to reduce recurrent ischemic events in CABG patients, and this hypothesis warrants confirmatory evidence from future, appropriately designed, randomized clinical trials.

Reprint requests and correspondence: Dr. David J. Whellan, Division of Cardiology, Thomas Jefferson University Hospital, 1015 Chestnut Street, Suite 317, Philadelphia, Pennsylvania 19107. E-mail: djw150@jefferson.edu.

REFERENCES

1. Nathoe HM, van Dijk D, Jansen EW, et al. A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. N Engl J Med 2003;348:394–402.
2. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
3. Fabricius AM, Gerber W, Hanke M, Garbade J, Autschbach R, Mohr FW. Early angiographic control of perioperative ischemia after coronary artery bypass grafting. Eur J Cardiothorac Surg 2001;19:853–8.
4. Boyle EM Jr., Lille ST, Allaire E, Clowes AW, Verrier ED. Endothelial cell injury in cardiovascular surgery: atherosclerosis. Ann Thorac Surg 1997;63:885–94.
5. Reilly CF, McFall RC. Platelet-derived growth factor and transforming growth factor-beta regulate plasminogen activator inhibitor-1 synthesis in vascular smooth muscle cells. J Biol Chem 1991;266:9419–27.
6. Verrier ED, Boyle EM Jr. Endothelial cell injury in cardiovascular surgery. Ann Thorac Surg 1996;62:915–22.
7. Nachman RL, Silverstein R. Hypercoagulable states. Ann Intern Med 1993;119:819–27.
8. Ishiwata S, Tukada T, Nakanishi S, Nishiyama S, Seki A. Post-angioplasty restenosis: platelet activation and the coagulation-fibrinolysis system as possible factors in the pathogenesis of restenosis. Am Heart J 1997;133:387–92.
9. Goldman S, Copeland J, Moritz T, et al. Long-term graft patency (3 years) after coronary artery surgery. Effects of aspirin: results of a VA cooperative study. Circulation 1994;89:1138–43.
10. Gavaghan TP, Gebski V, Baron DW. Immediate postoperative aspirin improves vein graft patency early and late after coronary artery bypass graft surgery. A placebo-controlled, randomized study. Circulation 1991;83:1526–33.
11. Zimmermann N, Wenk A, Kim U, et al. Functional and biochemical evaluation of platelet aspirin resistance after coronary artery bypass surgery. Circulation 2003;108:542–7.
12. Mangano DT. Multicenter Study of Perioperative Ischemia Research Group. Aspirin and mortality from coronary bypass surgery. N Engl J Med 2002;347:1309–17.

13. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494–502.
14. Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial. Circulation 2004;110:1202–8.
15. Held C, Asenblad N, Bassand JP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol 2011;57:672–84.
16. Varenhorst C, Alström U, Scirica BM, et al. Factors contributing to the lower mortality with ticagrelor compared with clopidogrel in patients undergoing coronary artery bypass surgery. J Am Coll Cardiol 2012;60:1623–30.
17. Tricoci P, Roe MT, Mulgund J, et al. Clopidogrel to treat patients with non-ST-segment elevation acute coronary syndromes after hospital discharge. Arch Intern Med 2006;166:806–11.
18. Biancari F, Airaksinen KE, Lip GY. Benefits and risks of using clopidogrel before coronary artery bypass surgery: systematic review and meta-analysis of randomized trials and observational studies. J Thorac Cardiovasc Surg 2012;143:665–75.
19. Raivio P, Kuitunen A, Suojaranta-Ylinen R, Lassila R, Petäjä J. Thrombin generation during reperfusion after coronary artery bypass surgery associates with postoperative myocardial damage. J Thromb Haemost 2006;4:1523–9.
20. Lison S, Dietrich W, Braun S, et al. Enhanced thrombin generation after cardiopulmonary bypass surgery. Anesth Analg 2011;112:37–45.
21. Leonardi S, Tricoci P, Mahaffey KW. Promises of PAR-1 inhibition in acute coronary syndrome. Curr Cardiol Rep 2012;14:32–9.
22. Chintala M, Vemulapalli S, Kurowski S, et al. SCH 530348, a novel oral antiplatelet agent, demonstrated no bleeding risk alone or in combination with aspirin and clopidogrel in cynomolgus monkeys (abstr). Arterioscler Thromb Vasc Biol 2008;28:e138–9.
23. Tricoci P, Huang Z, Held C, et al. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. N Engl J Med 2012;366:20–33.
24. Morrow DA, Braunwald E, Bonaca MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. N Engl J Med 2012;366:1404–13.
25. TRA*CER Executive and Steering Committees. The Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRA*CER) trial: study design and rationale. Am Heart J 2009;158:327–34.
26. Boisclair MD, Lane DA, Philippou H, Sheikh S, Hunt B. Thrombin production, inactivation and expression during open heart surgery measured by assays for activation fragments including a new ELISA for prothrombin fragment F1 + 2. Thromb Haemost 1993;70:253–8.
27. Petäjä J, Pesonen E, Fernández JA, Vento AE, Rämö OJ, Griffin JH. Cardiopulmonary bypass and activation of antithrombotic plasma protein C. J Thorac Cardiovasc Surg 1999;118:422–9, discussion 429–31.
28. Kulik A, Le May MR, Voisine P, et al. Aspirin plus clopidogrel versus aspirin alone after coronary artery bypass grafting: the Clopidogrel After Surgery for Coronary Artery Disease (CASCADE) trial. Circulation 2010;122:2680–7.
29. de Leon N, Jackevicius CA. Use of aspirin and clopidogrel after coronary artery bypass graft surgery. Ann Pharmacother 2012;46:678–87.
30. Gao G, Zheng Z, Pi Y, Lu B, Lu J, Hu S. Aspirin plus clopidogrel therapy increases early venous graft patency after coronary artery bypass surgery: a single-center, randomized, controlled trial. J Am Coll Cardiol 2010;56:1639–43.
31. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;58:e123–210.
32. Smith PK, Goodnough LT, Levy JH, et al. Mortality benefit with prasugrel in the TRITON-TIMI 38 coronary artery bypass grafting cohort: risk-adjusted retrospective data analysis. J Am Coll Cardiol 2012;60:388–96.
33. Becker RC, Moliterno DJ, Jennings LK, et al. Safety and tolerability of SCH 530348 in patients undergoing non-urgent percutaneous coronary intervention: a randomised, double-blind, placebo-controlled phase II study. Lancet 2009;373:919–28.
34. Judge HM, Jennings LK, Moliterno DJ, et al. PAR-1 antagonists inhibit thrombin-induced platelet activation whilst leaving the PAR4-mediated response intact. Paper presented at: XXIV Congress of the International Society on Thrombosis and Haemostasis; June 29 to July 4, 2013; Amsterdam, the Netherlands. Available at: http://www.eventure-online.com/eventure/publicAbstractView.do?id=215172&congressId=6839. Accessed May 1, 2013.
35. Cornelissen I, Palmer D, David T, et al. Roles and interactions among protease-activated receptors and P2ry12 in hemostasis and thrombosis. Proc Natl Acad Sci U S A 2010;107:18605–10.
36. Lopes RD, Hafley GE, Allen KB, et al. Endoscopic versus open vein-graft harvesting in coronary-artery bypass surgery. N Engl J Med 2009;361:235–44.
37. Shroyer AL, Grover FL, Hattler B, et al. On-pump versus off-pump coronary-artery bypass surgery. N Engl J Med 2009;361:1827–37.

Key Words: bypass ■ coronary disease ■ myocardial infarction ■ platelets ■ thrombin.