Study design and rationale of a comparison of prasugrel and clopidogrel in medically managed patients with unstable angina/non–ST-segment elevation myocardial infarction: The TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medically manage Acute Coronary Syndromes (TRILOGY ACS) trial

Chee Tang Chin, MBChB, a Matthew T. Roe, MD, MHS, a Keith A. A. Fox, MBChB, b Dorairaj Prabhakaran, MD, c Debra A. Marshall, MD, d Helene Petitjean, MD, e Yuliya Lokhnygina, PhD, a Eileen Brown, PhD, d Paul W. Armstrong, MD, f Harvey D. White, MD, g and E. Magnus Ohman, MD a on behalf of the TRILOGY ACS Steering Committee Durham, NC; Edinburgh, United Kingdom; New Delhi, India; Indianapolis, IN; Parsippany, NJ; Alberta, Canada; and Auckland, New Zealand

Practice guidelines recommend dual antiplatelet therapy with aspirin and clopidogrel for patients with non–ST-segment elevation acute coronary syndromes (NSTE ACS) regardless of in-hospital management strategy. Prasugrel—a thienopyridine adenosine diphosphate receptor antagonist that provides higher and less variable levels of platelet inhibition than clopidogrel—has demonstrated benefit when used to treat ACS patients undergoing percutaneous coronary intervention. However, the optimal approach to antiplatelet therapy for high-risk, medically managed NSTE ACS patients remains uncertain, as these patients have not been the focus of previous clinical trials of these therapies. TRILOGY ACS is a phase 3, randomized, double-blind trial enrolling approximately 10,300 NSTE ACS patients within 10 days of presentation with either unstable angina or NSTE myocardial infarction who are not intended to undergo revascularization procedures for their index event. Patients will be randomly allocated to prasugrel + aspirin versus clopidogrel + aspirin for a median duration of 18 months. A reduction in the maintenance dose of prasugrel for elderly patients (age ≥75 years) and those with body weight <60 kg is planned. The primary composite efficacy end point will be time to first occurrence of cardiovascular death, myocardial infarction, or stroke in patients aged <75 years. If the superiority of prasugrel is established in patients aged <75 years, the treatment arms will then be compared for all subjects (including those aged ≥75 years). TRILOGY ACS is the largest randomized clinical trial to date focusing exclusively on medically managed NSTE ACS patients and will provide important information regarding the optimal approach to oral antiplatelet therapy for this high-risk, understudied population. (Am Heart J 2010;160:16-22.e1.)

Background

Effective antiplatelet therapy is critical for reducing atherothrombotic complications associated with acute coronary syndrome (ACS).1 Practice guidelines recommend combination therapy with aspirin and a thienopyridine such as clopidogrel for non–ST-segment elevation (NSTE) ACS patients regardless of in-hospital management strategy.2,3

In observational studies worldwide, approximately half of all unstable angina (UA) and NSTE myocardial infarction (NSTEMI) (collectively known as NSTE ACS)

From the "Duke Clinical Research Institute, Durham, NC, bRoyal Infirmary of Edinburgh, Edinburgh, United Kingdom, cCentre for Chronic Disease Control, New Delhi, India, dEli Lilly and Company, Indianapolis, IN, eDaichi Sankyo, Inc, Parsippany, NJ, fUniversity of Alberta, Edmonton, Alberta, Canada, and gGreen Lane Cardiovascular Service, Auckland City Hospital, Auckland, New Zealand. www.clinicaltrials.gov Identifier: NCT00699998.
Submitted February 8, 2010; accepted April 29, 2010. Reprint requests: Matthew T. Roe, MD, MHS, 2400 Pratt St, Room 7035, Duke Clinical Research Institute, Durham, NC 27705. Email: matthew.roe@duke.edu.
0002-8703/$ - see front matter © 2010, Mosby, Inc. All rights reserved. doi:10.1016/j.ahj.2010.04.022
patients do not undergo revascularization during the initial hospitalization. Medically managed NSTE ACS patients may have comorbidities that are contraindications to coronary angiography or may have complex anatomy that precludes revascularization. In clinical trial populations and observational registries, these patients have more high-risk features than patients undergoing revascularization; consequently, medically managed NSTE ACS patients also have worse outcomes.

The combination of clopidogrel and aspirin among medically managed NSTE ACS patients improves both short- and long-term outcomes. Despite these data and despite guidelines recommending dual antiplatelet therapy for all NSTE ACS patients, clopidogrel remains underused in the medically managed population. However, enhanced platelet inhibition appears to be particularly important in these patients because they seem to have more adverse events after premature discontinuation of clopidogrel compared with patients who undergo percutaneous coronary intervention (PCI). Nonetheless, there is variability in patient responsiveness to clopidogrel, leading to inadequate platelet inhibition and an increased risk for atherothrombotic events in patients shown to have reduced responsiveness.

Prasugrel (CS-747, LY640315) is a third-generation thienopyridine adenosine diphosphate P2Y12-receptor antagonist that has been demonstrated to have more potency and less response variability than clopidogrel. In the TRITON trial, ACS patients undergoing PCI who received prasugrel (loading dose [LD] 60 mg and maintenance dose [MD] 10 mg daily) had fewer ischemic events compared with patients receiving clopidogrel, including fewer spontaneous MI occurring ≥30 days after randomization. However, the risk of bleeding events was higher in patients receiving prasugrel compared with clopidogrel. In the PLATO study, ACS patients who received ticagrelor, another more potent and consistent P2Y12-receptor inhibitor, had improved outcomes compared with patients receiving clopidogrel. However, ticagrelor was associated with increased rates of non-coronary artery bypass graft surgery (CABG)-related and intracranial hemorrhage. The TRITON and PLATO trials collectively demonstrated that more potent and consistent P2Y12 receptor inhibition reduced the risk of atherothrombotic events, albeit at an increased risk of bleeding—a finding that is especially pertinent to the treatment of medically managed NSTE ACS patients, who typical have a greater burden of comorbidities that predispose to bleeding.

Given the significant proportion of NSTE ACS patients managed medically worldwide and the need to mitigate both ischemic and bleeding risks in this vulnerable, high-risk population, novel clinical trials are needed. The TaRgeted platelet Inhibition to cLarinify the Optimal strateGy to medically manag e ACS (TRILOGY ACS) trial is distinct from previous ACS trials because it will (1) be the first trial of tailored therapeutics with an antiplatelet agent post-ACS (reduced prasugrel MD for elderly and/or low-weight patients at higher risk for bleeding), (2) study the longest treatment duration with a thienopyridine post ACS (median treatment duration 18 months), and (3) address an unmet medical need by specifically evaluating the understudied medically managed NSTE ACS population.

Methods

Study organization

TRILOGY ACS is a phase 3, randomized, double-blind, double-dummy, active-controlled study being conducted at nearly 800 sites worldwide. The academic members of the executive committee, in collaboration with representatives from the trial sponsors, designed TRILOGY ACS. The executive and operations (steering) committees, which include academic members and sponsor representatives, oversee the medical, scientific, and operational conduct of the study. TRILOGY ACS adheres fully to the ethical principles of the Declaration of Helsinki, the specifications of the International Conference on Harmonization, and Good Clinical Practice, including the requirement for each subject’s informed consent before initiating any study procedure.

Study population

The TRILOGY ACS study population will consist of approximately 10,300 patients presenting within 10 days of a UA/NSTEMI event. Randomization is recommended only after a medical management strategy has been selected for a given patient with reasonable certainty. To ensure early thienopyridine treatment according to practice guidelines recommendations, all subjects will either be randomized or on a stable regimen of commercial clopidogrel within 72 hours of the index event. (stable regimen of clopidogrel is defined as having received a ≥300-mg LD within 72 hours of the index event followed by 75 mg daily OR having received 75 mg daily for ≥5 days before the index event and daily thereafter). Enrichment criteria derived from the GRACE mortality model were incorporated to define a high-risk population expected to derive the greatest benefit from the study treatments (Table I). Other inclusion and exclusion criteria are shown in Tables I and II.

A protocol amendment (Table III), completed in May 2009, was based on feedback from active sites and adopted after approximately 1,000 subjects were enrolled. The period to receive the commercial clopidogrel LD was extended, as sites were not administering clopidogrel within 24 hours of the index event because of concerns regarding increased perioperative bleeding risk should a patient require CABG once coronary anatomy was defined during angiography. Thus, 72 hours—upper limit specified in guidelines for performing early catheterization in NSTE ACS—was changed. The enrollment window was extended from 7 to 10 days because many sites were recruiting patients in the early postdischarge outpatient setting. Angiographic criteria and symptom duration were modified based on investigator feedback of the presentation profiles of their UA/NSTEMI patients and their common approach to performing revascularization for patients with coronary stenoses ≥50%. Finally, additional end points were added based upon feedback from regulatory authorities when
data from the TRITON trial became available after finalizing the initial protocol.

Study treatment

The study incorporates a double-blind, double-dummy design: prasugrel with matching placebo tablets and clopidogrel with matching placebo tablets. Randomization is stratified by age, country, and prior clopidogrel treatment status (Table IV and Figure 1). Study treatment is administered on a background of low-dose aspirin (daily dose between 75 and 100 mg is strongly recommended). Furthermore, all subjects are strongly recommended to receive other concomitant secondary prevention medications according to practice guidelines recommendations.2,5

Subjects not on a stable regimen of clopidogrel and randomized within 72 hours of the index event will initiate study treatment with a LD; otherwise, the first study drug dose administered will be either a MD of clopidogrel (75 mg) or prasugrel (5 or 10 mg). The prasugrel MD will depend upon age and body weight at randomization. Treatment will continue for a minimum of 6 months and a maximum of 30 months. Prior studies led to the selection of the 60-mg prasugrel LD in the TRITON trial to provide faster and greater platelet inhibition in a population undergoing PCI almost immediately after randomization.13 However, a 30-mg prasugrel LD was selected in TRILOGY ACS because it will still result in higher and faster levels of platelet inhibition compared with clopidogrel, but will potentially be associated with less acute bleeding risk in medically managed patients who do not need immediate, high-level platelet inhibition just after randomization.19

The prasugrel MDs selected for this trial were based on observations from the TRITON trial, in which elderly (age ≥75 years) and low–body-weight (<60 kg) subgroups were associated with increased bleeding risk. These patients have been shown to have a higher exposure to the active metabolite of prasugrel, which may explain the increased bleeding risk seen with the 10-mg MD.20 Therefore, subjects aged ≥75 years or <60 kg in weight will receive 5-mg prasugrel MD in an effort to reduce bleeding complications while preserving the efficacy of prasugrel.

Study objectives and end points

An independent clinical events adjudication committee will adjudicate all end point events as defined in Table V.
The primary objective of TRILOGY ACS is to test the hypothesis that the combination of prasugrel and aspirin is superior to the combination of clopidogrel and aspirin in the treatment of medically managed subjects enrolled within 10 days of the UA/NSTEMI index event. This will be assessed by comparing prasugrel with clopidogrel with respect to the time to first occurrence of the primary composite end point of cardiovascular death, MI, or stroke. The primary analysis will be conducted in a hierarchical manner, with evaluation of the primary end point performed first in subjects aged ≥75 years, the majority of whom will receive a 10-mg prasugrel MD. Conditional on establishing superiority in the primary analysis, the same composite end point will be evaluated in the entire population by including the patients aged ≥75 years.

Additional secondary efficacy composite end points include the first occurrence of: cardiovascular death or MI; cardiovascular death, MI, stroke, or rehospitalization for recurrent UA; all-
cause death, MI, or stroke; and stent thrombosis.22 Although TRILOGY ACS will enroll medically managed patients, rates of stent thrombosis will be examined per regulatory requirements because it is anticipated that some subjects will have undergone previous coronary stenting before the index ACS event or may undergo coronary stenting during study follow-up for a recurrent ischemic event.

Safety
The safety objectives are to evaluate the rates of bleeding as defined by GUSTO and TIMI criteria23-25 (Appendix A, online). This broad range of bleeding end points examined, including both fatal and intracranial bleeding, will enable better understanding of the bleeding risks in this high-risk, medically managed population. Because of a small numerical excess of non-benign neoplasms in the prasugrel-treated group in the TRITON trial (risk ratio 1.17, 95% CI 0.87-1.58, \( P = .30 \)), a prospective cancer surveillance plan will be implemented, including collecting data on baseline cancer risk factors, history of neoplasm at study entry, and results of cancer screening tests performed.26 Suspected new or recurrent non-benign neoplasms will be reported as safety end points during the study. Suspected new or recurrent non-benign neoplasm events will be adjudicated by an independent Oncology Clinical End Points Committee.

Safety monitoring
The independent external Data Monitoring Committee will convene and review blinded data (treatment A vs treatment B) every 6 months to evaluate interim efficacy and safety data during the trial. At all interim analyses, study termination will be considered if the data suggest a strong likelihood of excessive life-threatening bleeding or death in the prasugrel group compared with the clopidogrel group. There will be no formal consideration for stopping early because of efficacy; and therefore, no adjustment to the final \( \alpha \) level for efficacy testing will be made.

Platelet function substudy and genomic analyses
Approximately a third of subjects will participate in the platelet function substudy. At participating sites, all subjects will contribute to the pharmacodynamic, genomic, and biomarker components of the substudy. Subjects’ platelet function will be measured using the Accutronics (San Diego, CA) “VerifyNow P2Y12” and “VerifyNow Aspirin” assays at serial time points during the study. The pharmacodynamic component of the substudy will investigate the relationship of platelet function with ischemic and bleeding events, and allow pharmacodynamic comparison between treatment groups. Furthermore, baseline and 6-month serum samples for high-sensitivity C-reactive protein and N-terminal B-type natriuretic peptide will be collected.

Both clopidogrel and prasugrel require biotransformation to active metabolites by cytochrome P450 (CYP) enzymes.27-31 In contrast to prasugrel, genetic variants in CYP alleles, such as CYP2C19, significantly diminish the pharmacokinetic and pharmacodynamic responses to clopidogrel and are associated with increased rates of ischemic events.12,27 Therefore, DNA collection will be encouraged to assess the interaction between treatment groups and the genetic variation in drug-metabolizing enzymes, P2Y12 receptor polymorphisms, and transporters on platelet function, clinical efficacy, and safety outcomes. All patients in the platelet function substudy will have DNA samples collected at baseline, whereas patients not participating in the substudy will have the option of contributing to the voluntary DNA banking addendum.

Health outcomes substudy
Major health care resource use, medical costs, and incremental cost-effectiveness will be assessed as a function of treatment assignment and platelet function in certain countries participating in TRILOGY ACS. Health-related quality-of-life outcomes will also be assessed.

Statistical considerations
Sample size and data analysis. TRILOGY ACS is an event-driven trial and will enroll approximately 10,300 subjects worldwide (7,800 subjects aged ≤ 75 years and a maximum enrollment of 2,500 subjects aged ≥ 75 years) over a projected accrual period of 24 to 36 months with a maximum 30-month follow-up period, resulting in an approximately 18-month median follow-up. Balanced representation of subjects is expected worldwide. The sample size will provide 90% power to detect a 22% relative risk reduction between the 2 treatment arms using a 2-sided test at 5% significance level for subjects aged < 75 years. All subjects aged ≤ 75 years will be followed for at least 6 months; the study is designed to proceed until 688 subjects aged < 75 years experience an event of the primary end point. These calculations are based on (1) an 8% clopidogrel event rate for the primary end point in the first year followed by a 4% event rate during the second year (which we believe is a conservative estimate of event rates based upon subgroup analyses of medically managed patients enrolled in previous ACS trials)30,31 and (2) a 5% annual dropout rate. At least 2,000 subjects aged ≥ 75 years will be enrolled, regardless of the time of last subject enrollment in the age < 75 years cohort.

Statistical/analytical plans. The final statistical analysis plan has been submitted to the US Food and Drug Administration. Primary analyses will be conducted on end points adjudicated by the independent cardiology clinical events committee. Efficacy end point analyses will be carried out using the intent-to-treat population. The “as-treated” population, consisting of subjects receiving ≥ 1 dose of study drug (including LD), will be used for all safety end point analyses.

The primary end point is the composite of cardiovascular death, MI, or stroke. Time to the first occurrence of the primary end point will be compared between treatment groups using a stratified 2-sided log-rank test where the strata are subject categories per Table IV. The primary analysis will be carried out in a hierarchical manner. As a first step, treatment groups within the age < 75 years cohort will be compared. Upon establishing superiority of prasugrel over clopidogrel in the age < 75 years cohort, the treatment arms will be compared for all subjects using a stratified 2-sided log-rank test with 2 stratification variables: subject category per Table IV and age (< 75 or ≥ 75 years). A key secondary analysis will include a Cox proportional hazard model for time to first occurrence of the primary outcome with the covariates of age (as a continuous variable), NSTEMI versus UA, diabetes mellitus, and chronic
heart failure. To encompass repeated events, an Anderson-Gill intensity model will be used.29

Prespecified subgroup analyses will be carried out with a Cox proportion hazard model that contains an effect for treatment, subgroup variable, subgroup by treatment interaction, and stratification variable. Subgroups to be analyzed include, but are not limited to, NSTEMI versus UA, prior clopidogrel use versus no prior use, diabetes mellitus versus none, creatinine clearance <60 versus ≥60 mL/min, female versus male sex, geographic region, prior coronary revascularization versus none, GRACE risk score (patients below the median score vs above), age ≤65 versus >65 years, and frail versus nonfrail patients. Frail patients will be patients aged ≥65 years who fulfill a set of criteria (recorded and validated previously) at randomization.30 Time to first occurrence of GUSTO- and TIMI-defined bleeds (Appendix A, online) will be compared between treatment groups with a stratified log-rank test for those patients at risk. A patient is considered at risk during the period from first dose of study drug through 7 days after permanent study drug discontinuation. In addition, multivariate models will be carried out for key bleeding variables (GUSTO life-threatening or severe bleeding and TIMI major and minor bleeding). Analyses of bleeds and other safety outcomes will be done for subjects aged <75 years, all subjects, and subjects aged ≥75 years. A net clinical benefit end point will be evaluated incorporating all-cause death, MI, stroke, and GUSTO severe or life-threatening bleeding.

Current status
The first subject was enrolled in June 2008; as of March 2010, >3,500 subjects have been enrolled worldwide. The Data Monitoring Committee has met 3 times to review patient data and, on each occasion, recommended continuation of enrollment without further protocol alterations.

Funding
The TRILOGY ACS trial is sponsored by Eli Lilly and Company, Indianapolis, IN, and Daiichi Sankyo Co, Ltd, Tokyo, Japan. The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the paper, and its final contents.

Summary
TRILOGY ACS is a phase 3, multicenter, randomized, double-blind, active-controlled study designed to assess the efficacy and safety of prasugrel versus aspirin compared with clopidogrel and aspirin for the long-term management of high-risk, medically managed UA/NSTEMI patients. This trial will provide insight into whether more potent P2Y12 inhibition with prasugrel translates into improved outcomes for the long-term treatment of medically managed subjects post-ACS. TRILOGY ACS will be distinguished from previous ACS trials by addressing an unmet clinical need in the high-risk medically managed patient population. Moreover, it will be the longest study of post-ACS P2Y12 inhibition and will be the first trial to tailor a post-ACS antplatelet regimen by individualizing prasugrel dosing based on key patient characteristics.

Disclosures
Chee Tang Chin: none.
Keith Fox: research support/grants: Sanofi-aventis, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly & Company, Bayer; honoraria: Sanofi-aventis, GlaxoSmithKline.
Dorairaj Prabhakaran: research support/grants: Duke Clinical Research Institute, Eli Lilly & Company, Merck, Sharpe & Dohme, Unilever.
Helene Petitjean: employee of Daiichi Sankyo, Inc.
Yuliya Lokhnygina: none.

References


Appendix A. Safety end points and bleeding classification schemes according to GUSTO\textsuperscript{23} and TIMI\textsuperscript{24} criteria

- **Non-CABG-related GUSTO severe or life-threatening bleeding** is any intracranial hemorrhage (ICH) OR any bleeding event resulting in substantial hemodynamic compromise requiring treatment.
- **Non-CABG-related GUSTO moderate bleeding** is any bleeding event resulting in the need for transfusion that is not considered a GUSTO severe or life-threatening bleed.
- **Non-CABG-related GUSTO mild bleeding** is any other bleeding event that does not require transfusion or cause hemodynamic compromise.
- **Non-CABG-related TIMI major bleeding** is any ICH OR any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in hemoglobin (Hgb) of $\geq 5$ gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as 1 unit packed red blood cells [RBCs] = 1 gm/dL Hgb = 3% hematocrit [Hct]).
- **Non-CABG-related TIMI life-threatening bleeding** is any non-CABG-related TIMI major bleeding that is fatal, leads to hypotension that requires treatment with intravenous vasopressor agents, OR requires surgical intervention for ongoing bleeding, OR necessitates the transfusion of 4 or more units of blood (whole blood or packed RBCs) over a 48-hour period, OR any symptomatic ICH.
- **Non-CABG-related TIMI minor bleeding** is any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in Hgb of $\geq 3$ gm/dL, but $< 5$ gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as 1 unit packed RBCs = 1 gm/dL = 3% Hct).
- **Non-CABG-related TIMI minimal bleeding** is any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in Hgb of $< 3$ gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as 1 unit packed RBCs = 1 gm/dL = 3% Hct).

Additional safety end points include the following:

- Incidence of fatal bleeding or ICH.
- Incidence of CABG-related bleeding events.

---

Appendix B. Executive Committee, Data Monitoring Committee, and Steering Committee Members

Executive Committee Members: E. Magnus Ohman (chairman), Durham, NC; Matthew T. Roe (principal investigator), Durham, NC; Paul W. Armstrong, Edmonton, Alberta, Canada; Keith A. A. Fox, Edinburgh, United Kingdom; Debra A. Marshall, Indianapolis, IN; Helene Petitjean, Parsippany, NJ; Dorairaj Prabhakaran, New Delhi, India; Harvey D. White, Auckland, New Zealand.

Data Monitoring Committee Members: Frans Van de Werf (chairman), Leuven, Belgium; Andrzei Budaj, Warsaw, Poland; Bernard J. Gersh, Rochester, MN; Gilles Montalescot, Paris, France; Stuart J. Pocock, London, United Kingdom; Robert G. Wilcox, Nottingham, United Kingdom; David O. Williams, Providence, RI; Michael Wilson (independent statistician), Indianapolis, IN.

Steering Committee Members: Diego Ardissino, Parma, Italy; Philip E. Aylward, Adelaide, Australia; Jean-Pierre Bassand, Besancon, France; Deepak L. Bhatt, Boston, MA; William E. Boden, Buffalo, NY; Victor R. Castillo, Bucaramanga, Colombia; Terrance Chua, Singapore; Mircea Cintea, Bucharest, Romania; Peter Clemmensen, Copenhagen, Denmark; Ramon Corbalan, Santiago, Chile; Jan-Hein Cornel, Alkmaar, the Netherlands; Anthony J. Dalby, Johannesburg, South Africa; David Erlinge, Lund, Sweden; David Foley, Dublin, Ireland; Vladimir Gasparovic, Zagreb, Croatia; Shaun Goodman, Toronto, Ontario, Canada; Shmuel Gottlieb, Jerusalem, Israel; Assen Goudev, Sofia, Bulgaria; Nikolay Gratsiansky, Moscow, Russia; Paul Gurbel, Baltimore, MD; Christian W. Hamm, Bad Auheim, Germany; Judith S. Hochman, New York, NY; Kurt Huber, Vienna, Austria; Myung Ho Jeong, Dongku, Korea; Jose Luis Leiva-Pons, San Luis Potosi, Mexico; Jose Lopez-Sendon, Madrid, Spain; Thomas F. Luscher, Zurich, Switzerland; Felipe Martinez, Cordoba, Argentina; Darren K. McGuire, Dallas, TX; Bela Merkely, Budapest, Hungary; Walter Enrique Mogrovejo, Lima, Peru; Jose C. Nicolau, Sao Paulo, Brazil; Ali Oto, Ankara, Turkey; Gregory Pavlides, Athens, Greece; Luis Providencia, Coimbra, Portugal; Witold Ruzyllo, Warsaw, Poland; Piyamitr Sritara, Bangkok, Thailand; Mikko Syvanne, Helsinki, Finland; Grace Topacio, Manila, Philippines; Chuen-Den Tseng, Taipei, Taiwan; Freek Verheugt, Nijmegen, the Netherlands; Petr Widimsky, Prague, Czech Republic; Stephen D. Wiviott, Boston, MA; Robaayah Zambahari, Kuala Lumpur, Malaysia; Zhu Jun-Ren, Shanghai, China.

Cardiovascular Clinical Events Adjudication Committee: Rajendra Mehta (Chairman), Durham, NC.

Statistical Group: Eileen Brown, Indianapolis, IN; Yuliya Lokhnygina, Durham, NC; Stacy Woodard, Research Triangle Park, NC.