A Comparison of prasugrel at the time of percutaneous Coronary intervention or as pretreatment at the time of diagnosis in patients with non-ST-segment elevation myocardial infarction: Design and rationale for the ACCOAST study

Gilles Montalescot, MD, PhD, a,k Leonardo Bolognese, MD, b,k Dariusz Dudek, MD, PhD, c,k Patrick Goldstein, MD, d,k Christian Hamm, MD, e,k Jean-François Tanguay, MD, f,k Jur ten Berg, MD, PhD, g,k Petr Widimsky, MD, DrSc, h,k Junxiang Luo, PhD, i,k Debra L. Miller, RN, RCIS, i,k and Jochen Goedicke, MD, i,k Paris and Lille, France; Arezzo, Italy; Krakow, Poland; Bad Nauheim, and Hamburg, Germany; Montreal, Canada; Nieuwegein, The Netherlands; Prague, Czech Republic; and Indianapolis, IN

Background The precise risk/benefit of thienopyridine pretreatment and the optimal dosage and timing of a thienopyridine loading dose (LD) for patients presenting with non-ST-segment elevation (NSTE) acute coronary syndromes are still being debated. Prasugrel, a novel thienopyridine, is an appropriate drug to address this issue as it provides predictably high and rapid inhibition of platelet aggregation.

Study Design ACCOAST is a phase 3, multicenter, parallel-group, double-blind, and event-driven study designed to compare 2 prasugrel LD schedules in patients with NSTE myocardial infarction who are scheduled for coronary angiography/percutaneous coronary intervention (PCI). Approximately 4,100 patients will be randomly assigned to an initial LD of 30 mg of prasugrel after the diagnosis followed by coronary angiography with an additional dose of 30 mg of prasugrel given at the time of PCI (pretreatment) or an LD of 60 mg of prasugrel given to patients undergoing PCI at the time of the procedure (non-pretreatment). All patients undergoing PCI will receive 5 or 10 mg of prasugrel daily. The primary objective is to test the hypothesis that prasugrel pretreatment is superior to prasugrel non-pretreatment as measured by a reduction in the composite end point of cardiovascular death, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa inhibitor bailout through 7 days from randomization. Key safety end points include TIMI (Thrombolysis In Myocardial Infarction) major and minor bleeding risks.

Conclusions The ACCOAST study will provide important evidence with regard to the benefits and risks of prasugrel pretreatment compared with administration of prasugrel at the time of PCI in patients with NSTE myocardial infarction. (Am Heart J 2011;161:650-6)

From the "Hôpital de la Pitié-Salpêtrière, Paris, France, "San Donato Hospital, Arezzo, Italy, "University Hospital, Krakow, Poland, "University Hospital, Lille, France, "Kernhoff Heart and Thoracic Center, Bad Nauheim, Germany, "Montreal Heart Institute/Département de Médecine, Université de Montréal, Montreal, Canada, "St. Antonius Ziekenhuis, Nieuwegein, The Netherlands, "Third Faculty of Medicine, Charles University, Prague, Czech Republic, "Lilly Research Laboratories, Indianapolis, IN, and "Lilly Research Laboratories, Hamburg, Germany.

a,k for the ACCOAST investigators. RCT Reg. No. NCT01013287. Submitted June 27, 2010; accepted October 6, 2010. Reprint requests: Gilles Montalescot, MD, PhD, Institut de Cardiologie, Bureau 2236, Centre Hospitalier Universitaire Pitié-Salpêtrière, 47 Boulevard de l’Hôpital, 75013 Paris, France.

E-mail: gilles.montalescot@ap-hop.fr, siuol.paul4600@psl.aphp.fr

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Dual antiplatelet therapy with aspirin and a thienopyridine is standard for prevention of thrombotic complications after percutaneous coronary intervention (PCI) and recurrence of ischemic events in patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACSs). Pretreatment with a loading dose (LD) of 300 mg of clopidogrel immediately upon diagnosis of NSTE-ACSs followed by a daily maintenance dose (MD) of 75 mg is a level I-A recommendation of the 2007 European Society of Cardiology (ESC) guidelines. Results from the CURE study provide support for the ESC guidelines as the recommended clopidogrel dose in this study significantly reduced ischemic events compared with placebo. On the other hand, clopidogrel led to a significantly higher
rate of major bleeding. In addition, in the PCI-CURE substudy, the median treatment was 6 days prior to PCI.

Clinical trial data in the current ESC guidelines for NSTE-ACSs supporting the recommendation for clopidogrel pretreatment in patients to be managed with PCI consist of a non-randomized registry of clopidogrel pretreatment in patients with mostly stable angina, the TARGET study, comparing glycoprotein (GP) IIb/IIIa inhibitors in the setting of planned PCI in which clopidogrel pretreatment was not randomized, and the CREDO study, which failed to demonstrate that pretreatment with clopidogrel was superior to placebo in the reduction of ischemic events at 28 days after planned PCI. Data from a subgroup analysis from CREDO did, however, support the >6-hour timing for pretreatment with an LD of 300 mg of clopidogrel vs no LD in the setting of elective PCI or ACSs managed with PCI. A meta-analysis of 3 studies investigating the effects of clopidogrel pretreatment (PCI-CURE, CREDO, and PCI-CLARITY) identified a benefit in reducing ischemic events associated with an increase in TIMI (Thrombolysis In Myocardial Infarction) major and minor bleeding after PCI. The results of the PRAGUE-8 study, a clinical trial not yet included in PCI guidelines, demonstrated that pretreatment with the higher 600-mg clopidogrel LD does not reduce ischemic events but results in significantly more major plus minor bleeding in patients undergoing elective coronary angiography with ad hoc PCI.

Theoretically, the advantage of early administration of a thienopyridine LD for patients with unknown coronary artery anatomy prior to diagnostic coronary angiography is to achieve higher inhibition of platelet aggregation (IPA) and thus prevent recurrent atherothrombotic events in patients likely to undergo PCI. However, the optimal timing for administration of a thienopyridine LD remains a matter of debate. For example, the 2009 American College of Cardiology guidelines recommend that clopidogrel be given either before or at the time of PCI or that, if it is used, prasugrel be given at the time of PCI. In contrast, the 2007 ESC guidelines recommend immediate pretreatment with a thienopyridine LD. This discrepancy demonstrates the clear medical need for research to clarify optimal dosage and timing of administration of a thienopyridine LD for patients presenting with NSTE myocardial infarction (NSTEMI) who are scheduled for coronary angiography with the expectation of proceeding to a PCI.

Rationale for use of prasugrel in ACCOAST

Prasugrel is a novel thienopyridine prodrug that is more efficiently metabolized to its active metabolite than clopidogrel. It is a potent and effective inhibitor of adenosine diphosphate (ADP)-mediated platelet activation and aggregation mediated by the platelet P2Y12 ADP receptor that, compared with clopidogrel, provides enhanced IPA with less interpatient variability. When treated with prasugrel, common functional cytochrome P450 genetic variants do not affect active drug metabolite levels, IPA, or clinical cardiovascular (CV) event rates. In addition, genetic variation in ABCB1, a common ATP-binding cassette transporter, is not associated with a significant effect on IPA or clinical CV event rates in patients treated with prasugrel. In a study that compared a 60-mg prasugrel LD with a 600-mg clopidogrel LD, patients treated with clopidogrel had significantly lower mean IPA. Furthermore, a significantly large variability in response resulted in >25% of clopidogrel-treated patients, compared with no prasugrel-treated patients, being classified as hyporesponsive 6 hours after dosing.

Recent approvals of prasugrel in the European Union, United States, and Canada are largely based on results from the pivotal phase 3 TRITON-TIMI 38 study. This study showed that prasugrel treatment (60-mg LD/10-mg MD) resulted in a significantly greater reduction in the primary composite efficacy end point (death from CV causes, non-fatal myocardial infarction [MI], or non-fatal stroke) than the approved clopidogrel dosing regimen (300-mg LD/75-mg MD) in clopidogrel-naive patients with ACSs scheduled to undergo PCI. The reduction in ischemic events with prasugrel as compared with clopidogrel was, as expected, associated with a significant increase in the rate of bleeding. Exploratory analyses identified 3 subgroups as having increased risk of bleeding, including patients with a history of stroke or transient ischemic attack, patients ≥75 years old, or patients with a body weight <60 kg.

A substudy of TRITON-TIMI 38 prospectively enrolled a subset of patients to evaluate ADP-pattemated phosphorylation of platelet vasodilator-stimulated phosphoprotein (VASP) in order to show differences in platelet function between treatment arms. Prasugrel-treated patients had a significantly lower VASP platelet reactivity index and maximal platelet aggregation than clopidogrel-treated patients at 1-2 hours post-PCI and during maintenance dosing (30 days). Thienopyridine hyporesponsiveness (VASP platelet reactivity index ≥50%) was also significantly more frequent in clopidogrel-treated patients than in prasugrel-treated patients at 1-2 hours post-PCI and at 30 days.

The ongoing TRILOGY ACS study will evaluate the relative efficacy and safety of prasugrel and clopidogrel in patients with unstable angina/NSTEMI who will be medically managed and will not undergo a planned PCI procedure. In one stratum, TRILOGY ACS is studying a 30-mg prasugrel LD in medically managed patients who are clopidogrel-naive. In addition, TRILOGY ACS is incorporating a 5-mg prasugrel MD for patients weighing <60 kg or are ≥75 years old. ACCOAST will complement both TRITON-TIMI 38 and TRILOGY by incorporating the prasugrel LDs and MDs used in both trials.
The ACCOAST study is designed to compare pretreatment with prasugrel to that with ticlopidine as studied in the NSTEMI cohort of TRITON-TIMI 38 for patients expected to undergo PCI. Study patients in both treatment arms who undergo PCI will all have received a total of 60 mg of prasugrel at the time of PCI. ACCOAST will provide evidence to determine whether a pretreatment dosing strategy will reduce the incidence of periprocedural ischemic events compared with administration of prasugrel at the time of PCI in the high-risk NSTEMI population. The pretreatment window will be restricted to a maximum of 48 hours prior to coronary angiography/PCI, reflecting recent data obtained regarding timing of intervention in TIMACS, ABOARD, and ACUITY and consistent with modern practice in high-volume centers.

Methods
Study objectives

The primary objective is to test the hypothesis that initiation of the prasugrel LD at the time of a qualifying diagnosis of NSTEMI with elevated troponin and prior to coronary angiography is superior to initiation of the prasugrel LD at the time of the PCI procedure, as measured by a reduction in the composite end point of CV death, MI, stroke, urgent revascularization (UR), or GP IIb/IIIa inhibitor bailout through 7 days from randomization.

A key secondary efficacy hypothesis is that early administration of the prasugrel LD will also provide net clinical benefit (reduction in the composite of all-cause death, MI, stroke, or all coronary artery bypass graft [CABG] and non-CABG TIMI major bleeding) through 7 days from randomization. Additional efficacy objectives will compare the 2 prasugrel LD regimens in terms of CV death alone and combined with one or more individual components of the primary composite end point (MI, stroke, or UR), definite or probable stent thrombosis, and net clinical benefit through 30 days from randomization. Additional safety objectives will evaluate all CABG or non-CABG TIMI major bleeding through 7 days, as well as through 30 days from randomization.

Substudies

Blood samples that may be used for genetic testing will also be collected. DNA derived from these samples may be used to determine the influence of genetic variants on drug metabolism, transport, treatment response, efficacy, adverse events, or risk of CV events.

In addition, an intensive platelet monitoring substudy will be conducted to further explore the IPA of prasugrel in patients with NSTEMI who undergo PCI. The primary analysis will evaluate the time course of IPA in the non-pretreatment arm in which patients receive a 60-mg prasugrel LD at the time of PCI in the cardiac catheterization laboratory.

Several prespecified subgroup analyses of primary and secondary efficacy end points and key safety end points will be performed. These analyses will be conducted according to the following criteria: (1) PCI vs medically managed vs CABG surgery; (2) clopidogrel use prior to randomization; (3) time of randomization from symptom onset; (4) time of PCI (or coronary angiography) from randomization; (5) Global Registry of Acute Coronary Events hospital admission risk score; (6) diabetes status; (7) baseline creatinine status; and (8) qualifying troponin level at study entry. Additional exploratory analyses of prespecified study end points will include comparisons within patient characteristics, baseline comorbid conditions, procedure and study drug-related variables, and concomitant medications. Other exploratory analyses will include time to first occurrence of GUSTO Bleeding Criteria and STEEP Bleeding Criteria.

Study design and population

ACCOAST (www.clinicaltrials.gov no. NCT01015287) is a phase 3, randomized, parallel-group, double-blind, placebo-controlled, and 2-arm trial to be conducted at >100 sites in >10 countries. This is an event-driven study that will continue until 400 patients have experienced a primary efficacy end-point event, estimated to occur when approximately 4,100 patients (2,050 in each arm) have received study treatment. Patients must meet eligibility criteria (online Appendix A), including having a diagnosis of NSTEMI (defined as a history of chest discomfort or ischemic symptoms of ≥10 minutes' duration at rest ≤48 hours prior to entry into the study with no evidence of persistent ST-segment elevation) with elevated troponin (≥2.5 times the upper limit of normal according to local laboratory norms), and should be scheduled to undergo coronary angiography/PCI within 24 hours of randomization. If necessary due to timing constraints, the procedure may be scheduled the next day, but definitely no more than 48 hours from randomization. Exclusion criteria include having a medical history considered a contraindication for therapy with prasugrel (eg, history of stroke or transient ischemic attack) and undergoing treatment with any thienopyridine LD or a ticlopidine or prasugrel MD within 7 days of study entry. Patients may be receiving a 75-mg clopidogrel MD if they are able to switch to prasugrel during the study.

Treatment protocol and follow-up procedures

Investigators will determine eligibility and obtain patient informed consent prior to performing any study procedures. Patients will be randomly assigned to 1 of 2 treatment arms in a parallel, 1:1 manner, at the site level (Figure 1). The initial LD of the study drug will be administered as soon as possible after randomization. The second blinded LD of the study drug will be administered after completion of coronary angiography and the decision to proceed with PCI. The first open-label prasugrel MD will be administered 18-24 hours post-PCI. Assessment of clinical end points and adverse events will take place prior to, during, and after coronary angiography/PCI, at hospital discharge, on day 30, and via telephone on day 90.

If the coronary angiography reveals an anatomy that is not amenable to PCI, the patient will not undergo PCI or receive the second LD. Any subsequent thienopyridine therapy (open-label clopidogrel or ticlopidine) for patients who are medically managed or who proceed to CABG surgery will be left to the investigators' discretion.

Dosing regimen

All patients who undergo PCI will receive a total prasugrel LD of 60 mg, with the pretreatment arm having a split LD of
Concomitant medications

Adjuvant aspirin (75 to 325 mg oral or 250 to 500 mg intravenous) will be administered, per investigator discretion, along with the initial LD of the study drug in ACCOAST. The Summary of Product Characteristics recommends daily adjuvant 75 to 325 mg aspirin daily with prasugrel maintenance therapy. Antithrombin therapy during PCI is recommended as standard of care; the specific type and dose to be administered in ACCOAST will be determined by the treating investigator.

Use of a GP IIb/IIIa inhibitor at the time of screening or randomization is an exclusion criterion; however, any planned use prior to or during PCI is allowed.

Study end points

The primary efficacy measure is a composite of CV death, MI, stroke, UR, or GP IIb/IIIa inhibitor bailout through 7 days from randomization. As results from TRITON-TIMI 38 showed a benefit within the initial 3 days for prasugrel-treated, vs clopidogrel-treated, patients, the 7-day time point was specifically chosen to investigate the early effects of pretreatment with prasugrel. Cardiovascular death includes death with a demonstrable CV cause, or any death that is not clearly attributable to a non-CV cause. To be considered a primary end point event, an MI must be distinct from the index event. Definitions of MI (Table I) include an adapted version of the universal definition of MI using creatine kinase (CK) or CK-myocardial bands (CK-MB) and depend on the clinical timing of the event in relation to the timing of the index event and CV procedures. In addition, a definition is included for determination of MI as a primary ACCOAST end point under circumstances in which cardiac biomarkers were not obtained. Stroke is defined as a rapid onset of a new persistent, neurological deficit that lasts for more than 24 hours. The definition of UR is driven by symptoms of ischemia that worsen and require catheterization prior to the planned coronary angiography/PCI or recurrent signs of ischemia occurring after completion of the planned PCI, leading to a new emergent revascularization (PCI or CABG surgery) of either the vessel dilated at the initial procedure or a vessel not initially dilated. The unplanned use of a GP IIb/IIIa inhibitor while waiting for coronary angiography/PCI, during PCI, or within 24 hours after PCI will be considered as bailout. This is a novel end point designed to provide information regarding reasons for and the specific timing of GP IIb/IIIa bailout during thienopyridine treatment of patients with NSTEMI.

Secondary efficacy measures include all-cause death (any death due to cardiac or non-cardiac cause) and stent thrombosis. Stent thrombosis is based on Academic Research Consortium definitions and comprises angiographic or pathological confirmation, as well as clinical determination of stent thrombosis. Major safety end points of TIMI major, life-threatening, and minor bleeding (online Appendix B) will be evaluated in terms of CABG surgery-related, non-CABG surgery-related, and all bleeding.

Statistical considerations

Determination of sample size

ACCOAST is designed to continue until 400 patients reach one of the primary efficacy end-point events within 7 days of randomization, requiring an anticipated enrollment of 4,100 patients. The study will provide 80% power to establish the superiority of prasugrel pretreatment (LD given at time of diagnosis) to non-pretreatment (LD given at time of PCI) relative to the primary composite end point. These calculations are based on the following assumptions: (1) 11% of patients...
in the prasugrel non-pretreatment arm having a primary end-point event within 7 days of randomization based on extrapolations from the TRITON-TIMI 38, ISAR-REACT 2, and EARLY ACS studies; (2) an average hazard ratio (HR) of 0.753; and (3) the time-to-first event analysis based on a 2-sided log-rank test used at a 2-sided significance level (α) of 0.05 to assess superiority. It is expected that 80% of the patients in ACCOAST will undergo PCI, 18% will be medically managed, and 2% will require CABG surgery.

Statistical and analytical plans

Reaching any component of a composite end point will be considered as reaching that end point. Efficacy analyses will utilize the intent-to-treat data set, which consists of all randomized patients. Safety analyses will include all patients who receive at least one dose of the study drug (including placebo). Safety analyses will focus on events (including bleeding events, other treatment-emergent adverse events, or abnormal laboratory values) that occur during the period from administration of the first dose of the study drug through 7 days after permanent study drug discontinuation or the discontinuation visit, whichever is earlier.

Primary and secondary efficacy analyses will be based on time from randomization to onset of the first occurrence of the event using a 2-sided log-rank test. Corresponding survival curves will be estimated by the Kaplan-Meier method. The 2-sided 95% confidence intervals for the HR will be provided via a Cox proportional hazard model, which will also be conducted to evaluate non-inferiority; the prasugrel pretreatment group will be considered non-inferior to the non-pretreatment group in net clinical benefit if the upper limit of the 1-sided 95% confidence intervals for the HR is below the non-inferiority margin of 1.1. The individual component of composite end points will be compared between the 2 prasugrel LD regimens by using time-to-first event analysis or Pearson’s χ² test.

Study organization

ACCOAST is sponsored by Daiichi Sankyo Co, Ltd (Tokyo, Japan) and Eli Lilly and Company (Lilly, Indianapolis, Ind, USA). The ACCOAST Steering Committee, which includes academic members and Lilly representatives, is solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing this and forthcoming manuscripts. The steering committee will have full access to the final study data, including actual patient data and statistical programming.

An independent clinical end points committee will adjudicate efficacy end-point events as well as TIMI major and minor bleeding events in a blinded fashion. An independent statistical analysis center, whose members are external to the sponsor, will provide safety data reports and statistical analyses. Safety monitoring, as well as one planned interim analysis, will be conducted by an independent, external data monitoring committee. Lilly has contracted with ICON Clinical Research to provide site management, i3 Statprobe to provide data management services, and Tata Consultancy Services to provide statistical programming.

Summary

ACCOAST is a multicenter, randomized, parallel-group, and double-blind study designed to compare 2 prasugrel LD schedules in patients with NSTEMI with elevated troponin who are scheduled for coronary angiography/PCI. To date, there are no other prospective randomized trials designed to study thienopyridine pretreatment compared with the same thienopyridine treatment given at the time of PCI in a high-risk NSTEMI population. This trial will provide important information
regarding the benefits and risks of pretreatment with prasugrel, a thienopyridine that achieves a predictably high and rapid IPA.

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References
