Trial Designs

Comparison of Prasugrel and Bivalirudin vs Clopidogrel and Heparin in Patients With ST-Segment Elevation Myocardial Infarction: Design and Rationale of the Bavarian Reperfusion Alternatives Evaluation (BRAVE) 4 Trial

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ABSTRACT

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy for patients with ST-segment elevation myocardial infarction (STEMI). Effective and safe adjunct antithrombotic therapy is a major determinant for short- and long-term outcomes after primary PCI. Two separate studies have shown significant benefits vs conventional therapy for 2 recently approved drugs. In the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, bivalirudin after pretreatment with clopidogrel resulted in improved net clinical outcome compared with heparin plus glycoprotein IIb/IIIa inhibitors. However, during the first 24 hours after PCI, there was an increase in stent thrombosis rates with bivalirudin. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel — Thrombolysis In Myocardial Infarction (TRITON-TIMI) 38 trial, prasugrel was superior to clopidogrel in patients with acute coronary syndrome with and without ST-segment elevation. The synergic actions of prasugrel and bivalirudin may maximize the benefit of antithrombotic therapy for STEMI patients undergoing primary PCI. However, no specifically designed studies have so far compared the combination of prasugrel plus bivalirudin with that of clopidogrel plus unfractionated heparin in these patients. The Bavarian Reperfusion Alternatives Evaluation (BRAVE) 4 study is a randomized, open-label, multicenter trial aimed to test the hypothesis that a strategy based on prasugrel plus bivalirudin is superior to a strategy based on clopidogrel plus unfractionated heparin in terms of net clinical outcome in STEMI patients with planned primary PCI.

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H. Schunkert reports lecture fees and meeting travel support from AstraZeneca, The Medicines Company, Bristol-Myers Squibb, and Sanofi-Aventis. The other coauthors report no conflict of interest.

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Introduction

Primary percutaneous coronary intervention (PCI) with stent implantation is the preferred reperfusion strategy for patients presenting with acute ST-segment elevation myocardial infarction (STEMI).[1] Adjunct antithrombotic pharmacotherapy is critical for the safe and efficacious performance of PCI. The introduction of dual antiplatelet therapy with acetylsalicylic acid (ASA) and the thienopyridine ticlopidine resulted in a drastic reduction in periprocedural stent thrombosis rates and bleeding complications compared with a regimen with heparin and warfarin derivatives.[2–4] However, the use of ticlopidine in primary PCI is limited by its delayed onset of action and adverse side effects. Glycoprotein (GP) IIb/IIIa inhibitors are characterized by a faster and more potent antiplatelet effect compared with the thienopyridine ticlopidine and were soon included in the armamentarium of adjunct antithrombotic treatment. Since the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial in 1998,[5] the peri-interventional administration of the GP IIb/IIIa inhibitor abciximab became an integral part of PCI, particularly in patients presenting with acute coronary syndrome (ACS). In several clinical trials of STEMI patients, abciximab in addition to ASA and ticlopidine more frequently restored (Thrombolysis In Myocardial Infarction [TIMI] grade) blood flow in the occluded artery as well as improved left ventricular function and reduced short- and long-term thrombotic complications.[6–9] However, the new-generation thienopyridine clopidogrel overcame the limitation of slow onset of ticlopidine, which requires at least 48 hours before achieving its maximal platelet inhibitory action.[10,11] Whereas in the pre-clopidogrel era, GP IIb/IIIa inhibitors had an established role in periprocedural therapy, several double-blind trials reevaluated adjunct GP IIb/IIIa inhibition in a broad spectrum of patients undergoing PCI after pretreatment with 600 mg clopidogrel. In fact, in the Bavarian Reperfusion Alternatives Evaluation (BRAVE) 3 trial, patients with STEMI presenting within 24 hours of symptom onset and receiving 600 mg clopidogrel did not benefit from upstream administration of abciximab in terms of reduction in infarct size.[12]

These data support the adjunct use of high-dose clopidogrel and unfractionated heparin in primary PCI, which have been the most common antithrombotic therapies in this setting.

Recently, 2 newly approved drugs have shown significant benefits in clinical outcome in large randomized clinical trials: the direct thrombin inhibitor bivalirudin[13] and the third-generation thienopyridine prasugrel.[14]

The randomized, open-label Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial compared anticoagulation with bivalirudin alone with a regimen of heparin plus GP IIb/IIIa inhibitors in 3602 STEMI patients undergoing primary PCI. More than 90% of patients were pretreated with either 300 mg or 600 mg clopidogrel. At 30 days, the use of bivalirudin was associated with improved net clinical outcomes (9.2% vs 12.1%; relative risk: 0.76, 95% confidence interval [CI]: 0.63-0.92, $P = 0.005$). The reduction was mainly driven by a lower rate of bleeding (4.9% vs 8.3%; relative risk: 0.60, 95% CI: 0.46-0.77, $P < 0.001$). Moreover, bivalirudin reduced short- and long-term cardiac and overall mortality.[13,15] Concerns arose due to a higher incidence of stent thrombosis within the first 24 hours after primary PCI with bivalirudin.[13] Moreover, the recent results of the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) trial[16] regarding the increased risk of stent thrombosis with bivalirudin again showed that we still need further research for the definition of the best bivalirudin-based strategy.

Secondly, the third-generation thienopyridine prasugrel has overcome some of the limitations of clopidogrel, such as a wide interindividual dose–response variability with a high on-treatment platelet reactivity in 15% to 30% of patients and a delayed onset of action.[17] Prasugrel provides a faster, more potent, and more consistent platelet inhibition compared with its predecessor, clopidogrel.[18] This seems to be of special importance in STEMI patients, which show higher rates of high on-treatment platelet reactivity and a more delayed onset of action of clopidogrel[19] but also third-generation adenosine diphosphate (ADP) receptor blockers.[20,21] In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) trial of 13 608 patients with ACS, prasugrel was superior to clopidogrel regarding the composite ischemic endpoint of cardiovascular death, myocardial infarction (MI), or stroke (9.9% vs 12.1%; hazard ratio for prasugrel vs clopidogrel: 0.81, 95% CI: 0.73-0.90, $P < 0.001$).[14] In particular, there was significant reduction in stent thrombosis with prasugrel in the STEMI subgroup (1.1% vs 2.5%; hazard ratio: 0.44, 95% CI: 0.22-0.87, $P = 0.0144$).[22] Of note, in STEMI patients the risk of non-CABG related bleeding was not increased with prasugrel compared with clopidogrel.[22]

Thus, bivalirudin and prasugrel may have synergic actions regarding their antithrombotic efficacy and safety profile. The combination of both drugs may have the potential to maximize the benefit of adjunct antithrombotic therapy for STEMI patients undergoing primary PCI.[23,24] However, no specifically designed trials have so far compared the combination of prasugrel plus bivalirudin with that of clopidogrel plus unfractionated heparin in these patients.

The objective of the current randomized controlled trial, therefore, is to test the hypothesis that in STEMI patients undergoing primary PCI, prasugrel plus bivalirudin is superior to clopidogrel plus heparin in terms of net clinical outcome (the composite of death, recurrent MI, unplanned infarct-related artery revascularization, stroke, definite stent thrombosis, or major bleeding).

Methods

Trial Design

The BRAVE 4 trial is a randomized, open-label, multicenter trial. The study population will consist of STEMI patients randomly assigned to either treatment with prasugrel plus bivalirudin or clopidogrel plus heparin. The Figure 1 provides a schema of the study design.

Entry Criteria

Patients are eligible for enrollment if they present with STEMI within 24 hours of symptom onset and primary PCI

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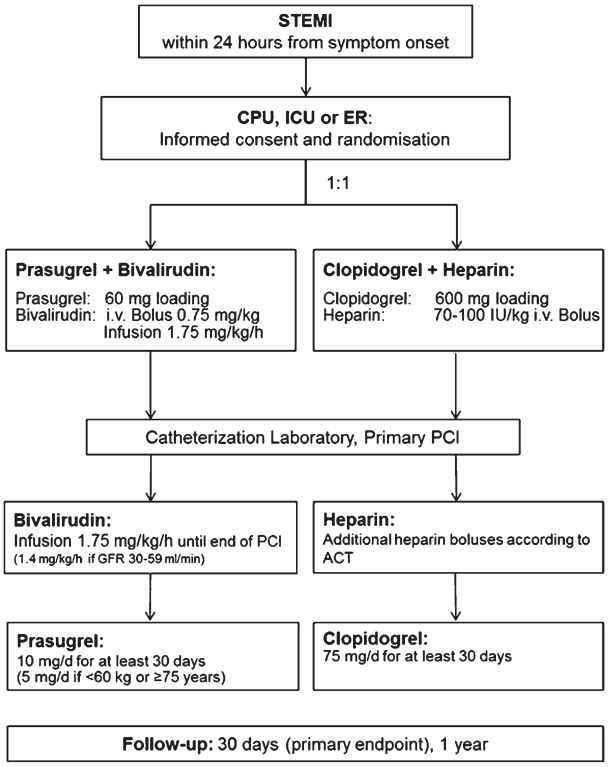

Figure 1. Study design. Abbreviations: ACT, activated clotting time; CPU, chest pain unit; ER, emergency room (department); GFR, glomerular filtration rate; ICU, intensive care unit; i.v., intravenous; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

is planned. The Table 1 summarizes the inclusion and exclusion criteria.

Treatment Regimen

This is an open-label study, and commercially available drugs will be given. Therapy with prasugrel plus bivalirudin or clopidogrel plus heparin will be administered immediately after randomization on the admitting ward (intensive care unit, chest pain unit, or emergency department).

Patients Randomized to Prasugrel Plus Bivalirudin: Prasugrel is administered with a loading dose of 60 mg orally. Those patients who have received a loading dose of clopidogrel for the index event will receive a reduced loading dose of 30 mg prasugrel. At the time the BRAVE 4 trial was designed, the reduction in the prasugrel loading dose from 60 to 30 mg in clopidogrel-loaded patients was motivated to prevent excess bleeding.[25] Recent platelet-function data confirm the adequacy of both the 30-mg and the 60-mg prasugrel loading doses in patients that have already received 600 mg clopidogrel. However, safety data in this regard are still lacking.[26] Prasugrel maintenance dose will consist of 10 mg daily and 5 mg daily for patients age ≥75 years or with body weight <60 kg, respectively.

Therapy with bivalirudin will be started with an intravenous (IV) bolus of 0.75 mg/kg of body weight followed by an infusion of 1.75 mg/kg/h for the duration of PCI. In patients with known moderate renal failure (glomerular filtration rate 30–59 mL/min), bivalirudin infusion will be reduced to 1.4 mg/kg/h. In patients with recent heparin administration, the time interval from the heparin bolus to the bivalirudin bolus should be ≥30 minutes.

Patients Randomized to Clopidogrel Plus Heparin: Therapy with clopidogrel is initiated with a loading dose of 600 mg

Table 1. Eligibility Criteria

Inclusion criteria
Patients presenting within 24 hours from the onset of symptoms, with chest pain lasting ≥20 minutes and with ≥0.1 mV of ST-segment elevation in ≥2 adjacent limb leads or ≥0.2 mV in ≥2 contiguous precordial leads or new LBBB
Informed written consent
In women with childbearing potential, a pregnancy test is obligatory.
Exclusion criteria
Age <18 years
Cardiogenic shock or prolonged CPR
Active bleeding, bleeding diathesis, coagulopathy
History of GI or genitourinary bleeding within the previous 2 months
Refusal to receive blood transfusion
Major surgery in the last 6 weeks
History of intracranial bleeding or structural abnormalities (intracerebral mass, aneurysm, AVM)
Suspected aortic dissection
Prior TIA, prior stroke
Heparin-induced thrombocytopenia
Prior administration of thrombolytics, bivalirudin, LMWH, or fondaparinux for the index MI
Known relevant hematological deviations: Hg <100 g/L, platelet count $<100 \times 10^9$ cells/L
Use of coumadin derivatives within the last 7 days
Chronic therapy with NSAIDs (except aspirin), COX-2 inhibitors, prasugrel, ticagrelor
Known malignancies or other comorbid conditions with life expectancy <1 year that may result in protocol noncompliance
Known severe liver disease
Known severe renal failure with GFR <30 mL/min and/or dialysis
Known allergy to the study medications
Previous enrollment in this trial
Women who are known to be pregnant, who are of childbearing potential and test positive for pregnancy, who have given birth within the last 90 days, who are breastfeeding
Inability to fully cooperate with the study protocol

Abbreviations: AVM, arteriovenous malformation; COX-2, cyclo oxygenase-2; CPR, cardiopulmonary resuscitation; GFR, glomerular filtration rate; GI, gastrointestinal; Hg, hemoglobin; LBBB, left bundle branch block; LMWH, low-molecular-weight heparin; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drugs; TIA, transient ischemic attack.

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and continued with a maintenance dose of ≥75 mg orally. In cases where clopidogrel has been administered prior to randomization, it is recommended that the new loading dose be reduced to the difference between 600 mg and the dose already given. Although unfractionated heparin is recommended, low-molecular-weight heparin (LMWH) is allowed according to local standards of the participating center. However, in situations where unfractionated heparin has been administered, switching to LMWH during primary PCI is not permitted. Prior administration of LMWH for the index MI is an exclusion criterion. Unfractionated heparin will be administered as an IV bolus of 70–100 IU/kg of body weight. Repeated activated clotting time (ACT) controls during primary PCI are not mandated per protocol. However, if unfractionated heparin has been administered before randomization, the subsequent boluses of heparin should be given ACT-guided (target ACT, 250–300 seconds).

The protocol-mandated duration of the randomized thienopyridine maintenance therapy with either prasugrel or clopidogrel is for ≥30 days after randomization. After 30 days, prasugrel or clopidogrel can be continued or switched to another thienopyridine (clopidogrel 75 mg per day or ticlopidine 500 mg per day). The protocol-mandated minimal duration of any thienopyridine therapy is for 6 months after randomization. In patients who do not undergo primary PCI, thienopyridine use is at the discretion of the treating physician.

Need for Bailout Antithrombotic Drugs: In the presence of abundant thrombotic material or sustained no reflow (TIMI flow 0–1), the following bailout strategies can be considered: either continuation of bivalirudin infusion after primary PCI for up to 12 hours (with dose reduction to a rate of 0.25 mg/kg/h after 4 hours) or the use of GP IIb/IIIa inhibitors in either group. The type of GP IIb/IIIa inhibitor used is left to the discretion of the operator.

Concomitant Medication: Acetylsalicylic acid 325 mg orally or 500 mg IV will be given immediately to all patients. After primary PCI, the daily dose of ASA will be 75 to 325 mg, indefinitely. Other medications will be given according to the judgment of the patient's physician.

Follow-up

All patients will be evaluated at the following time points: during the hospital stay, at 1 month (+7 days), and at 12 months (±14 days) after randomization. After the hospital stay, patients will be contacted by office visit, telephone, or letter. Detailed information regarding endpoints, adverse events, and patient compliance will be collected. If patients suffer an event at a different hospital, the appropriate source documents will be solicited.

Statistical Analysis

Key Endpoints: The primary endpoint is the composite of all-cause death, recurrent MI, definite stent thrombosis,[27] stroke, unplanned revascularization of the infarct-related artery, or major bleeding (HORIZONS-AMI definition)[13] at 30 days after randomization.

Secondary endpoints are the composite of all-cause death, recurrent MI, definite stent thrombosis,[27] stroke, or unplanned revascularization of the infarct-related artery (composite ischemic endpoint), the incidence of major bleeding complications,[13] and the incidence of cardiac death at 30 days after randomization. Bleeding events will also be evaluated according to the Thrombolysis In Myocardial Infarction (TIMI) criteria.[28] Appendix 1 shows a detailed description of the endpoint definitions.

Sample-Size Calculation: Sample-size calculation was based on the Fisher exact test with a 1-sided significance level of 2.5%, a power of 80%, and an assumed incidence of the primary endpoint of 12.1% with the strategy of clopidogrel plus heparin and 7.2% with the strategy of prasugrel and bivalirudin.[13,22] Accordingly, 601 patients in each group are needed. Compensation for losses to follow-up will require enrollment of a total of 1240 patients. After recruitment of 50% of the planned total number of patients, the event rates will be determined (blinded) and a reassessment regarding the total sample size will be performed.

Subgroup Analysis: Endpoint analysis will be performed in prespecified subgroups defined by age, sex, presence of diabetes mellitus, body mass index, pre-randomization heparin use, pre-randomization clopidogrel use, time interval from symptom onset to primary PCI, and time interval from thienopyridine administration (prasugrel or clopidogrel) to primary PCI.

Major Analytic Plan: Categorical variables such as demographics and medical-history data will be summarized using frequencies and proportions and will be compared using the χ^2 test or Fisher exact test, as appropriate. Continuous data will be summarized using mean ± SD or median (25th, 75th percentiles) and will be compared using the Student t test or nonparametric Wilcoxon rank-sum test. Cumulative event rates will be evaluated by the Kaplan-Meier estimator, and corresponding comparisons between the 2 study groups will be performed by means of the log-rank test. All analyses will be performed in a blinded manner regarding the randomly assigned treatment and on an intention-to-treat (ITT) basis. The main analysis will be performed by testing superiority in terms of primary endpoint at 30 days after randomization. Therefore, the Fisher exact test with a 1-sided significance level of 2.5% will be applied. Corresponding tests for other endpoints will be 2-sided, with $P < 0.05$ considered statistically significant.

Randomization: Randomization will take place on the admitting ward (intensive care unit, chest pain unit, or emergency department) of the participating centers. Randomization will be performed between prasugrel plus bivalirudin and clopidogrel plus heparin with a randomization ratio of 1:1. Allocation to treatment will be made by means of sealed opaque envelopes containing a computer-generated sequence, originated in the coordinating center (ISARe-search Center, Munich, Germany). Randomization will be stratified by study center and status of clopidogrel preloading. Randomly permuted block lengths will be used. The 2 treatment groups will be studied concurrently. Time zero is defined as the time of randomization. Patients will be considered enrolled in the study and eligible for the final ITT analysis at the time of randomization.

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Ethical Considerations: The study will be conducted in accordance with the provisions of the Declaration of Helsinki, the Good Clinical Practices of the International Conference on Harmonisation, and applicable local requirements.

Prior to participation in the study, the investigator will inform the patient orally and in writing about the scope and purpose, rights, duties, and possible risks and benefits of the study in lay language. Patients must be informed that their records will be subject to review by monitors or regulatory-agency representatives. They must also be assured that they may withdraw from the study at any time for any reason. The patient must authorize the release of his medical data by signing the patient informed-consent form.

Each investigator must obtain medical ethics committee approval for the protocol and informed-consent form prior to participation in this study. Further, any amendments to the protocol, as well as associated changes of the informed-consent form, will be submitted to the ethics committee and written approval must be obtained prior to implementation.

Substudy: The objective of the substudy is to compare the antiplatelet and anticoagulation efficacy of bivalirudin plus prasugrel vs clopidogrel plus heparin and to correlate the results with clinical outcomes. Platelet function tests include impedance aggregometry (Multiplate analyzer; F. Hoffmann-La Roche Ltd., Mannheim, Germany) using ADP, arachidonic acid, thrombin receptor activating peptide, and collagen as activating agents, as well as light transmission aggregometry (Born) using ADP and collagen as activating agents. Furthermore, an in vitro assay to measure platelet adhesion to collagen under flow is used. Coagulation tests include partial thromboplastin time as well as international normalized ratio. In addition, thrombelastography is used to test coagulation as well as clot formation and platelet function.

Organizational Structure: The authors are solely responsible for the design, conduct, data analyses as well as drafting and editing of the manuscript and its final content. Details about the organizational structure of the trial are shown in Appendix 2.

Discussion

In separate trials, prasugrel was shown to be superior to clopidogrel in the subset of STEMI patients[22] and bivalirudin superior to the combination of unfractionated heparin plus GP IIb/IIIa inhibitors in STEMI patients treated with clopidogrel.[13] These results led to a class I recommendation of prasugrel and bivalirudin in STEMI patients.[1] However, no specifically designed studies have so far compared the combination of prasugrel plus bivalirudin with that of clopidogrel plus unfractionated heparin in these patients. Therefore, the BRAVE 4 trial has the potential of providing the unique answer as to whether or not the combination of prasugrel plus bivalirudin will meet the great expectations.

In a large study, periprocedural MI and bleeding had a comparable prognostic value on 1-year mortality.[29] Thus, we chose a primary endpoint that includes both ischemic and bleeding complications. However, ischemic and bleeding endpoints are also important secondary endpoints of the trial, which will allow appreciation of the specific effects of the therapy on each of the components.

Although a double-blind, double-dummy trial would have been desirable, the associated financial and logistical efforts associated with this design were not feasible within this investigator-initiated trial lacking extramural funding. To avoid or minimize bias introduced by the open-label design, the following measures will be undertaken: the primary endpoint will be analyzed according to the ITT principle, there will be precise use of definitions for endpoint assessment, and core labs will be blinded, as will the adjudication of endpoint events by specialized Event Adjudication Committee members, relying on original source data. Thus, no information about study treatment will be provided. This will be of special importance for the adjudication of more subjective endpoints.

There is no precise evidence to substantiate the assumptions for sample-size calculation, and this is exactly the rationale for the BRAVE 4 trial. However, we acknowledge that the assumed risk reduction associated with prasugrel plus bivalirudin might be overenthusiastic.

Conclusion

The BRAVE 4 trial is an investigator-initiated, randomized, open-label, multicenter trial. The objective is to assess whether a regimen consisting of the third-generation thienopyridine prasugrel plus the direct thrombin inhibitor bivalirudin is superior to a conventional regimen of the second-generation thienopyridine clopidogrel plus unfractionated heparin in STEMI patients with planned primary PCI.

Appendix 1: Endpoint Definitions

Death[27]

Cardiac death: Any death due to proximate cardiac cause (eg, myocardial infarction [MI], low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment, will be classified as cardiac death.

Vascular death: Death caused by noncoronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases.

Noncardiovascular death: Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

All deaths are considered cardiac unless an unequivocal noncardiac cause can be established.

Myocardial Infarction

The definition of recurrent MI is based on the definitions of the Thrombolysis In Myocardial Infarction (TIMI) study group,[30] with a modification of the threshold for cardiac biomarker increase from 50% to 20% in patients for whom biomarkers of the index MI are falling but remain elevated (adapted from the Universal Definition of Myocardial Infarction).[31]

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Diagnosis of recurrent infarction will be based on the following criteria:

If the Biomarkers of the Index MI Are Still Increasing or the Peak Has Not Been Reached: The patients have to have both new electrocardiographic (ECG) changes consistent with MI (new or re-elevation of ST segments ≥0.2 mV in ≥2 contiguous precordial leads, ≥0.1 mV in ≥2 adjacent limb ECG leads, or development of new, abnormal Q waves considered distinct from the evolution of the index MI) and recurrent ischemic discomfort lasting ≥20 minutes at rest or ischemia-triggered hemodynamic instability;

If the Biomarkers of the Index MI Are Falling on Two Samples But Still Above the Upper Limit of Normal: The patients have to have either an increase in creatine kinase-MB >20% 3 to 6 hours after the second blood sample or new ECG changes consistent with MI (see above).

Stroke

Diagnosis of stroke requires confirmation by cardiac computed tomography, magnetic resonance imaging, or pathological confirmation.

Stent Thrombosis[27]

Stent thrombosis (ST) will be defined according to the Academic Research Consortium (ARC) definition of definite stent thrombosis, as presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion.

Acute ST: Occurring within 24 hours following the index PCI.

Subacute ST: 24 hours to 30 days following the index PCI.

Late ST: 31 to 360 days following the index PCI.

Very Late ST: >360 days following the index PCI.

Early ST includes acute and subacute events (0–30 days following the index PCI).

Infarct-Related Artery Revascularization

Infarct-related artery revascularization is defined as any ischemia-driven bypass surgery or repeat PCI of any lesion of the vessel that supplies the myocardial area of the index MI. The target vessel is one of the 3 main epicardial coronary arteries or bypass graft that contains the target lesion.

Bleeding[13,28]

Bleeding localization, amount of hemoglobin (Hb) and hematocrit (Hct) drop, and the number of blood units transfused will be recorded. Bleeding complications will be adjudicated as either related to or unrelated to bypass-graft surgery.

Major Bleeding According to HORIZONS-AMI:[13] Intracranial bleeding, intraocular bleeding, retroperitoneal bleeding, access-site hemorrhage requiring surgery or a radiologic or interventional procedure, hematoma ≥5 cm in diameter at the puncture site, reduction in Hb concentration of ≥4 g/dL without an overt source of bleeding, reduction in Hb concentration of ≥3 g/dL with an overt source of bleeding, reoperation for bleeding, or use of any blood-product transfusion.

Major Bleeding According to TIMI:[28] Intracranial or clinically significant overt signs of hemorrhage associated with a drop of in Hb of >5 g/dL or an absolute drop in Hct of >15% (when Hb is not available).

Minor Bleeding According to TIMI: Observed blood loss and a drop in Hb of 3 to ≤5 g/dL (if a Hb value was not available, a fall in the Hct of 9%– ≤ 15%), or a drop of ≥4 g/dL in Hb (or ≥12% in Hct) if no bleeding site was identifiable.

To account for transfusion, Hb and Hct measurements will be adjusted for any packed red blood cells or whole blood given between baseline and posttransfusion measurements. A transfusion of 1 unit of blood will be assumed to result in an increase of 1 g/dL in Hb or of 3% in Hct. If there has been an intervening transfusion between 2 blood measurements, the true change in Hb or Hct must be calculated:

$$\Delta\text{Hb} = [\text{baseline Hb} - \text{posttransfusion Hb}] + [\text{no. of transfused units}]$$

$$\Delta\text{Hct} = [\text{baseline Hct} - \text{posttransfusion Hct}] + [\text{no. of transfused units} \times 3]$$

Appendix 2: Study Organizational Structure

Steering Committee: A. Kastrati (Chairman), J. Mehilli (Principal Investigator), G. Richardt, R. Mehran, A. Gershlick

Project Management: S. Schulz, G. Schömig, B. von Merzljak, J. Luckmann, J. Ruf

Data Coordinating Center: ISAResearch Center Munich, H. Holle, F. Maimer-Rodrigues, H. Paul, M. Schulz, J. Vogel, N. Rifatov, K. Hoesl, I. Pastor, T. Morath, J. Neudecker, K. Mayer

Data and Safety Monitoring Board: F. Hofmann (Chair), J. Mann, D. Hauschke (Biostatistician)

Event Adjudication Committee: C. Schmitt (Chair), D. Poci, P. Barthel, G. Ndrepepa, D. Keta

Angiographic Core Laboratory: R. Byrne, S. Kufner, S. Piniek, S. Hurt, S. Kastrati

ECG Core Laboratory: K. Anette Fiedler

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