Evaluation of individualized clopidogrel therapy after drug-eluting stent implantation in patients with high residual platelet reactivity: Design and rationale of the GRAVITAS trial

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Background The inhibitory response to clopidogrel varies widely among individuals. Data suggest that patients with high residual platelet reactivity despite clopidogrel therapy are at greater risk for thrombotic events after percutaneous coronary intervention (PCI) with drug-eluting stents (DES). The Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS) trial is designed to evaluate whether tailored clopidogrel therapy using a point-of-care platelet function assay reduces major adverse cardiovascular events after DES implantation.

Study Design GRAVITAS is an international, randomized, multicenter, double-blinded, placebo-controlled, clinical trial. Approximately 2,800 patients with stable angina/ischemia or non–ST-elevation acute coronary syndrome undergoing PCI with DES will be enrolled. Patients with high residual platelet reactivity on clopidogrel therapy 12 to 24 hours post-PCI will be randomized to standard maintenance clopidogrel therapy (75 mg daily) or high-dose clopidogrel therapy (additional loading dose followed by 150 mg daily) for 6 months. A random sample of patients without high residual reactivity will be followed and treated with standard clopidogrel therapy for 6 months. The primary end point is the time to first occurrence of cardiovascular death, nonfatal myocardial infarction, or definite/probable stent thrombosis. Platelet function analyses will also be performed at 30 days and 6 months. Major safety end points include GUSTO severe and moderate bleeding unrelated to coronary artery bypass surgery.

Conclusions GRAVITAS is the first large-scale clinical trial designed to examine whether adjustment of clopidogrel therapy on the basis of platelet function testing using a point-of-care assay safely improves outcomes after PCI with DES. (Am Heart J 2009;157:818-824.e1.)

Clopidogrel is a thienopyridine that inhibits the platelet P2Y₁₂ ADP receptor, resulting in the inhibition of platelet activation and aggregation. Dual antiplatelet therapy with aspirin and a thienopyridine is the standard therapy for prevention of thrombotic complications after percutaneous coronary intervention (PCI). The phenomenon of late drug-eluting stent (DES) thrombosis has underscored the importance of prolonged and effective antiplatelet therapy after DES implantation.

The wide interindividual variability in the inhibitory response to clopidogrel is also well established. Observational studies have demonstrated that high residual platelet reactivity after clopidogrel therapy is associated with short- and long-term adverse events after PCI, including DES thrombosis. More powerful and consistent inhibition of the P2Y₁₂ receptor reduces cardiovascular events after PCI for acute coronary syndrome (ACS). Traditional methods to measure platelet reactivity after clopidogrel exposure, such as light transmittance aggregometry or flow cytometric assessment of the phosphorylation status of vasodilator-stimulated phosphoprotein, require specialized technical skill and are not widely available. Point-of-care assays can potentially be integrated into routine clinical practice. It is not known, however, whether a strategy of assessing platelet function and adjusting the postprocedural antiplatelet regimen in patients with high residual platelet reactivity on clopidogrel treatment is safe and effective in reducing thrombotic events after DES.
We designed a multicenter, randomized trial to compare a high-dose with a standard-dose clopidogrel regimen in patients who have undergone DES implantation and who possess high residual platelet reactivity on clopidogrel therapy as measured by a currently available point-of-care platelet function assay.

**Study objectives**

The primary objective of the Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS) trial is to test the hypothesis that adjusting the dose of clopidogrel in patients with high residual platelet reactivity after PCI with DES implantation based on the Accumetrics VerifyNow assay (Accumetrics, Inc, San Diego, CA) will reduce the hazard rate for ischemic events (cardiovascular death, nonfatal myocardial infarction, and stent thrombosis) in the 6 months after randomization. A secondary objective is to test the hypothesis that patients with high residual platelet reactivity treated with the standard clopidogrel 75 mg/d will have a greater hazard rate for ischemic events than similarly treated patients without high residual reactivity.

**Study design**

GRAVITAS is a randomized, double-blinded, placebo-controlled clinical trial involving approximately 70 sites in the United States and Canada (Figure 1) that will enroll approximately 2,800 patients.

**Patient population**

Inclusion and exclusion criteria are listed in Tables I and II. The study population includes patients with...
Table I. Inclusion criteria

1. Males or females aged 18 y or older.
2. Patients undergoing possible PCI with planned use of at least one DES and without the planned use of a GPIIb/IIIa inhibitor.
3. The indication for the procedure may be stable angina or ischemia, unstable angina without ST changes, or non-ST-elevation ACS (unstable angina with ST depression, or a non–ST-elevation MI).
4. The ability to understand the requirements of the study.
5. The ability to comply with study procedures and protocol.
6. A female patient is eligible to enter the study if she is of child-bearing potential and not pregnant or nursing, or not of child-bearing potential.

Table II. Exclusion criteria

1. PCI within previous 30 d.
2. History of gastrointestinal bleeding within 6 m.
4. Ischemic stroke within 6 wk.
5. Any history of hemorrhagic stroke or subarachnoid hemorrhage.
6. Other bleeding diathesis, or considered by investigator to be at high-risk for bleeding on long-term clopidogrel therapy.
7. Planned elective cardiac or noncardiac surgery within 6 m.
8. Planned coumadin therapy.
9. Current or planned therapy with other thienopyridine class of ADP receptor inhibitors.
10. Severe allergy to stainless steel, contrast dye, unfractonated heparin, low molecular weight heparin, or bivalirudin that cannot be adequately premedicated.
11. Allergy to aspirin or clopidogrel.
12. Current enrollment in an investigational drug or device study that has not reached the time of the primary end point.
13. Periprocedural GPIIb/IIIa inhibitor use (within 30 d for abciximab or 5 d for tirofiban or epftibide).
14. Thrombocytopenia (platelet count <100K).
15. Anemia (hematocrit <30%).
16. Polycthemia (hematocrit >52%).
17. PCI with placement of at least one DES is not performed.
18. Planned staged PCI in the next 6 m postprocedure.
19. Unsuccessful PCI (postprocedure diameter stenosis >30% with less than TIMI-3 flow in any treated vessel).
20. Patients with inhospital STEMI before randomization and those who require a target vessel revascularization before randomization.
21. Patients with acute stent thrombosis before VerifyNow platelet function test is performed.
22. Failure to meet clopidogrel requirements
   - If clopidogrel naive (day of procedure): must receive 600 mg loading dose up to 2 h post-PCI.
   - If on maintenance (previous) clopidogrel the day of procedure:
     - Must have been on at least 7 days of 75 mg OR, if less than 7 d of therapy, must have received a loading dose of clopidogrel of at least 300 mg at the time that clopidogrel therapy was begun.
     - Must NOT have received an additional loading dose (>75 mg) other than their routine 75-mg daily dose the day of the procedure.
23. Major complication during or after PCI, defined as: procedural death, intraprocedural stent thrombosis, vessel perforation requiring treatment, prolonged hypotension, arrhythmias requiring cardioversion, temporary pacemaker insertion or intravenous antiarrhythmic agents, respiratory failure requiring intubation, vascular injury (pseudoaneurysm, arteriovenous shunt, or hematoma >5 cm), or significant bleeding (any blood transfusion, drop in hemoglobin post-PCI by ≥3 g/dL).

stable angina or ischemia, or non–ST-elevation ACS (ie, unstable angina and non–ST-elevation MI). Patients undergoing angiography with possible PCI with DES without planned glycoprotein (GP) IIb/IIIa inhibition will be screened. In addition, patients who have undergone PCI with DES without GPIIb/IIIa inhibition and fulfill the study inclusion/exclusion criteria may be screened if they can provide informed consent and a blood sample for platelet reactivity can be obtained within 24 h after the PCI procedure. Key exclusion criteria include periprocedural GPIIb/IIIa inhibition (because this interferes with the platelet function assay that measures P2Y12-mediated reactivity), bleeding diathesis, or hemorrhage before the assessment of platelet function.

Point-of-care platelet reactivity assay

The VerifyNow System is a turbidimetric-based optical detection system that measures platelet aggregation. It consists of an instrument and a disposable assay device. The instrument controls all assay sequencing, temperature, and reagent-sample mixing. The assay device contains a lyophilized preparation of human fibrinogen-coated beads, platelet activators, and buffer. The patient sample is whole blood, which is automatically dispensed to reduce the activation contribution from ADP binding to P2Y1 receptors. The instrument measures platelet-induced aggregation as an increase in light transmittance and uses a proprietary algorithm to report values in P2Y12 reaction units (PRU). With this assay, a higher PRU reflects greater P2Y12-mediated reactivity. The mean coefficient of variation of test precision has been reported to be 3.2% in patients with coronary artery disease. The assay has been well correlated with ADP-induced platelet aggregation as determined by light transmittance aggreometry. A second activator, iso-thrombin receptor–activating peptide (iso-TRAP), is incorporated into a second channel of the assay device (BASE). The ADP-PGE1 and iso-TRAP channels are calibrated so that the maximal aggregations are identical. The device provides an estimated inhibition (“VerifyNow % inhibition”) without a preclopidogrel sample by reporting the ratio of the results of the ADP-PGE1 and iso-TRAP channels. In the VerifyNow Aspirin assay, the platelet agonist is arachidonic acid and reactivity is reported as aspirin response units, and in the VerifyNow GPIIb/IIIa assay, the agonist is iso-TRAP and reactivity is reported as platelet aggregation units. In GRAVITAS, patient selection and randomization will be based on PRU. The VerifyNow device software has been modified for this study to provide the platelet function assay results in an encrypted fashion using alphanumerical characters in place of numerals.

Study procedures, randomization, and treatment groups

Platelet function assessment with the VerifyNow P2Y12, VerifyNow Aspirin, and VerifyNow IIb/IIIa is
performed 12 to 24 hours post-PCI. The encrypted PRU value is entered telephonically to a central interactive voice response system that decrypts the entered PRU value and assigns the patient to a treatment group.

**Patients with high residual platelet reactivity on clopidogrel therapy.** Patients with a PRU ≥ 230 at 12 to 24 hours post-PCI are randomized in a 1:1 ratio to either standard dose clopidogrel therapy (75 mg daily) or high-dose clopidogrel therapy (an initial total dose of 600 mg, followed by 150 mg daily). Randomization is stratified by ACS (unstable angina with ST depression or non-ST-elevation MI) and study site so that patients with ACS will be represented equally in both randomized study arms within each center. A permuted block randomization scheme will be used.

**Patients without high residual platelet reactivity on clopidogrel therapy.** A random sample of patients with PRU < 230 will be enrolled and assigned to standard dose clopidogrel therapy (75 mg daily). Initially, permuted blocks of size 8 will be used to select a random sample of 1 in 8 patients within each center. The number of patients without high residual platelet reactivity who are selected for enrollment will be monitored on an ongoing basis and the block size will be adjusted as necessary to obtain 583 patients in this group over the course of the enrollment period. Patients with PRU < 230 not selected to be part of the random sample are not followed. However, demographic and clinical characteristics will be collected in all patients who undergo platelet function testing.

Study drug is provided in a blinded fashion (matching placebo and active clopidogrel with identical packaging). Therefore, the patient, treating physician, and research staff are blinded to both the level of residual platelet reactivity and treatment assignment for all enrolled subjects because the platelet reactivity value is encrypted and matching placebo is used.

**Concomitant medications**

**Clopidogrel.** As randomization in this trial is based upon a single post-PCI platelet function measurement 12 to 24 hours post-PCI, the study requirements for periprocedural clopidogrel therapy are meant to ensure that all screened patients are near to or at their steady-state level of inhibition at the time of measurement. In patients who are clopidogrel naive the day of the procedure, a dose of 600 mg must be administered not later than 2 hours post-PCI. Patients already on clopidogrel therapy must have received clopidogrel 75 mg a day for at least 7 days, or, if less than 7 days, they must have received a loading dose of ≥300 mg at the time that clopidogrel therapy was begun. Patients already receiving clopidogrel may not receive another loading dose, as additional clopidogrel loading doses in patients on clopidogrel therapy may further suppress platelet reactivity, which could result in a 12- to 24-hour post-PCI platelet function measurement that does not accurately reflect platelet reactivity on standard clopidogrel therapy over follow-up.

**Aspirin.** The exact dose of aspirin after discharge is left to the treating physician, but is restricted to 75 mg to 162 mg daily. This dose of aspirin was chosen to reduce bleeding risk in patients on dual antiplatelet therapy and is consistent with the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions PCI guideline recommendation that supports the use of lower dose aspirin in patients at high risk for bleeding.

**Periprocedural anticoagulation.** The choice of intraprocedural anticoagulant is at the discretion of the operator; unfractionated heparin, enoxaparin, and bivalirudin are all permitted.

**Study drug administration**

Study drug administration begins as soon as possible after group assignment by the interactive voice response system. After the additional loading dose (either placebo or 450 mg), patients immediately take their first day’s daily dose of study drug (either clopidogrel 75 mg and placebo or clopidogrel 150 mg). Therefore, patients with high residual platelet reactivity randomized to the high-dose arm receive 600 mg of clopidogrel on the first day after PCI. A recently reported study demonstrated that in nonresponders, an additional 600 mg of clopidogrel, when followed by a 150-mg maintenance dose, quickly achieves a new steady-state of greater platelet inhibition.

**Follow-up**

Clinical follow-up occurs at 30 days and 6 months. VerifyNow P2Y12 and VerifyNow Aspirin assays are also performed at 30 days and 6 months after study enrollment.

**End points and definitions**

The primary end point of GRAVITAS is cardiovascular death, nonfatal MI, or definite/probable stent thrombosis. All deaths are considered cardiovascular unless an unequivocal noncardiovascular cause can be established. Hemorrhagic deaths will also be considered cardiovascular. Myocardial infarction will follow the American College of Cardiology definition. Stent thrombosis will follow the Academic Research Consortium definition. Patients with high residual platelet reactivity on clopidogrel therapy will be defined as those with a PRU ≥ 230 measured 12 to 24 hours after PCI. We anticipate that approximately one third of the patient population will have this level of residual platelet reactivity. Reactivity above this threshold has been associated with ischemic events after PCI. The population-based threshold of the upper tertile and this PRU level are generally consistent with other definitions of clopidogrel nonresponsiveness.
that have been associated with poor outcomes using other measurement techniques.3-5

Major safety end points include severe or moderate bleeding, using the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries definition, which includes fatal bleeding and primary intracranial hemorrhage.18

Statistical considerations

**Determination of sample size.** A total of 1,980 patients (990 patients per randomized group) is the minimum required to detect a 50% relative risk reduction (RRR) in the risk of the primary outcome with 80% power, assuming a 6-month event rate of 5.0%. The conservative assumption of 5.0% for the 6-month primary event rate in the group with high residual platelet reactivity treated with standard dosing and the anticipated RRR with high-dose therapy are derived from the Stent Anticoagulation Restenosis Study,19 Buonamici et al,6 and Price et al.7 Although in these trials the event rates in “responders” are on the order of 80% lower than that in “nonresponders,” we chose a smaller anticipated RRR in patients with high residual platelet reactivity randomized to high-dose clopidogrel because some patients with high residual reactivity on standard dosing may not have further suppression of reactivity with an increased maintenance dose.20

The sample size for the primary hypothesis is computed using a continuity-corrected $\chi^2$ test and a 2-sided significance level ($\alpha$) of .049 to assess superiority. An adjustment was made to the significance level to account for one interim analysis, providing a final $\alpha$ of .049. Based on the above assumptions for the event rates at 6 months, and with a sample size of 990 in each group, the power of a log-rank test is 82%, provided that a total of at least 68 events are observed. Given a 10% anticipated withdrawal rate at 6 months, 2,200 patients (1,100 patients in each group) will be needed to obtain 1,980 patients at 6 months.

For the secondary hypothesis (comparing the rate of the primary end point in patients with and without high residual platelet reactivity treated with standard clopidogrel therapy), under the same assumptions and an estimated 6-month event rate of 2% in patients without high residual reactivity, 524 subjects are required. This implies that, assuming a 10% withdrawal rate, 583 patients need to be enrolled in the group of patients without high residual platelet reactivity.

**Interim analyses.** A single interim efficacy analysis will be performed when 50% of the required number of ischemic events for the primary efficacy analysis has occurred. The study may be terminated early owing to overwhelming efficacy if the 1-sided $P$ value for the primary efficacy analysis is <.00153. The pooled number of events in the randomized groups will also be examined at the time of the interim analysis and/or before the completion of enrollment, without knowledge of the event rates in the individual treatment groups, and the sample size may be increased to obtain a total of 68 events at the final analysis.

**Planned analyses.** All efficacy analyses will be performed according to the intent-to-treat principle. Analyses will also be performed on the efficacy evaluable population, which will include intent-to-treat patients who adhere to all key protocol procedures. This population will be determined before data unblinding. Safety analyses will be conducted in the cohort of patients who received at least 1 dose of study drug. The primary efficacy analysis will compare the time to the first occurrence of the primary end point in the patients with high residual platelet reactivity randomized to the high-dose clopidogrel regimen compared with those patients with high residual platelet reactivity randomized to the standard regimen, using a log-rank test stratified by the presence of ACS. A secondary analysis will compare the time to the first occurrence of the primary end point in the patients with high residual platelet reactivity treated with the standard clopidogrel regimen compared with that of the patients without high residual platelet reactivity treated with the standard clopidogrel regimen. Multivariate analyses of these 2 comparisons will be performed using a Cox regression model with the following prespecified covariates: treatment group, age $\geq$ 75 years, diabetes mellitus, ACS, total stent length, vessel diameter, and renal insufficiency. The treatment effect for each comparison will also be analyzed for the following prespecified patient subgroups, using a separate Cox regression model to estimate the hazard ratio, along with the interaction $P$ value: gender, age $\geq$ 75 years, diabetes mellitus, ACS, $>$ 1 stent implanted, multivessel stenting, total stent length $\geq$ 28 mm, vessel diameter $<$ 3.0 mm, restenotic lesion, bifurcation lesion, chronic total occlusion, saphenous vein graft target lesion, renal insufficiency, and aspirin resistance (defined as an aspirin response unit $\geq$ 550). Landmark analyses will be performed with the prespecified windows of randomization to day 30 and from day 30 to the end of the trial. Prespecified exploratory analyses include, but are not limited to, the individual components of the primary end point; the effect of the different antiplatelet regimens on measurements of platelet function (eg, PRU) over time; and the relationship between different measurements of platelet function (aspirin response, GP IIb/IIIa activity, percent P2Y$_{12}$ inhibition, and PRU) and clinical outcomes using receiver-operating characteristic curve analysis. Net clinical events (a composite of the primary end point and GUSTO severe bleeding) will also be examined. A cost-effectiveness analysis will be performed.
Study funding
The GRAVITAS trial is sponsored by Accumetrics and is coordinated by Scripps Advanced Clinical Trials. Study drug is supplied by Bristol-Myers Squibb Sanofi-Aventis (Princeton, NJ) to Scripps Advanced Clinical Trials through an investigator-initiated grant. Bristol-Myers Squibb Sanofi-Aventis has no role in study design, study management, or data interpretation. Both Accumetrics and Bristol-Myers Squibb Sanofi-Aventis had the opportunity to review this manuscript and will have the opportunity to review the manuscript describing the trial results.

Study organization
An executive committee composed of experienced clinical investigators in interventional cardiology and antiplatelet therapy provides trial leadership (Appendix A, available online). Accumetrics has only nonvoting input in the executive committee. Synteract (San Diego, CA) serves as the contract research organization and provides data and site management services. A clinical events committee blinded to treatment assignment and independent of the trial sponsor will adjudicate primary end-point events. A data and safety monitoring board provides oversight regarding safety and futility issues and is responsible for reviewing the interim analysis during the study.

Timeline
The first patient was enrolled in June 2008. The anticipated duration of enrollment is approximately 18 months, although the sample size may be increased based on the event rates at the time of the planned interim analysis.

Discussion
The wide variability of the inhibitory response to clopidogrel between individuals is well established.2 Nonrandomized, observational studies have demonstrated an association between a poor response to, or high residual platelet reactivity after, clopidogrel and ischemic events after PCI.3-7 Point-of-care technology enables platelet function testing in a clinical setting. However, the clinical utility of platelet function testing has yet to be demonstrated in a prospective, randomized fashion. The GRAVITAS study is designed to examine whether adjustment of clopidogrel therapy on the basis of platelet function testing safely improves outcomes after PCI with DES.

In GRAVITAS, the level of residual platelet reactivity after clopidogrel exposure is used to identify patients at potentially high risk for post-PCI events. Alternative approaches would include using the inhibition of platelet aggregation or the VerifyNow P2Y12 assay surrogate for inhibition of platelet aggregation, the ratio of ADP-induced to iso-TRAP-induced aggregation measured after clopidogrel exposure. From a pathophysiological standpoint, however, residual or on-treatment reactivity has shown to be a better measure of risk.2,21 The residual platelet reactivity based upon the VerifyNow P2Y12 device (on-treatment PRU) has been significantly associated with post-PCI events in observational studies.7,22,23 Exploratory analyses in GRAVITAS that examine the relationship between percent inhibition according to the VerifyNow P2Y12 assay and patient outcome may help determine the relevance of this measurement approach on clinical outcomes. GRAVITAS will also provide further information regarding the relationship between aspirin response and clinical outcomes after PCI.

The timing of platelet function measurement relative to PCI varies considerably in the observational studies that have examined the association between clopidogrel responsiveness and clinical outcome. Preprocedure measurements of residual platelet reactivity after clopidogrel treatment may be difficult to integrate into clinical practice in North America, as a clopidogrel loading dose is infrequently administered before diagnostic angiography despite guideline recommendations.5 In GRAVITAS, measurement of residual platelet reactivity is performed 12 to 24 hours after PCI, which in most cases will be around the time of the routine morning blood draw before discharge. Therefore, GRAVITAS is designed to test a management strategy that is applicable within real-world North American clinical practice.

An additional loading dose followed by an increased maintenance dose of clopidogrel 150 mg daily is used in the GRAVITAS trial as the pharmacologic intervention in patients with high residual platelet reactivity. This dosing regimen is not approved by the Food and Drug Administration. A staggered double loading dose24 and an increased maintenance dose have been shown in relatively small studies to improve inhibition in unselected patients undergoing PCI24,25 and in patients with a suboptimal response to standard therapy.15,20,26 In a large-scale, randomized fashion, GRAVITAS will determine the magnitude of the additional inhibitory effect on platelet reactivity provided by increased maintenance dosing in patients with high residual reactivity on standard therapy and will examine whether the anticipated incremental effect translates into a significant reduction in thrombotic events after DES placement.

The secondary objectives of GRAVITAS have substantial clinical relevance. GRAVITAS will further test the hypothesis that high residual reactivity after PCI is predictive of risk over long-term follow-up. Furthermore, by monitoring platelet function at 30 days and 6 months after PCI, GRAVITAS will be the largest study yet performed to define the natural history of platelet reactivity on clopidogrel therapy over the 6 months after PCI.
Conclusions
GRAVITAS is a randomized, international, double-blinded, placebo-controlled, clinical trial of individualized clopidogrel therapy after PCI based on the results of a point-of-care platelet function assay. This trial will provide important information regarding the safety and efficacy of high-dose maintenance clopidogrel in patients with high residual reactivity on standard clopidogrel therapy. This is the first large-scale clinical trial to assess the utility of platelet function monitoring to improve clinical outcomes after DES implantation.

References


Appendix A. Trial Organization

Coordinating Center: Scripps Advanced Clinical Trials, La Jolla, CA

Executive Committee (voting members): Matthew J. Price (principal investigator), Peter S. Berger, Christopher P. Cannon, Paul S. Teirstein, Eric S. Topol

Canadian Principal Investigator: Jean-François Tanguay

Clinical Events Committee: David E. Kandzari (chair)

Data Safety Monitoring Committee. David P. Faxon (chair), E. Magnus Ohman, Charles S. Davis (statistician)

Contract Research Organization: Synteract, San Diego, CA