

Drug Class Review on Newer Antiplatelet Agents

Update #2: Preliminary Scan Report #2

June 2009

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update

Update #1, April 2007 (searches through May 2006)

Date of Last Preliminary Update Scan

Preliminary Update Scan #1: March 2008

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

Key Questions

1. For adult patients with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease, do antiplatelet drugs differ in effectiveness?
2. For adults with acute coronary syndromes or coronary revascularization via stenting or bypass grafting, prior ischemic stroke or transient ischemic attack, or symptomatic peripheral vascular disease, do antiplatelet drugs differ in safety or adverse events?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications (drug-drug interactions), comorbidities (drug-disease

interactions), or pregnancy for which a particular antiplatelet drug is more effective or associated with fewer adverse events?

Inclusion Criteria

Based on the Key Questions, our review of the medical literature was designed to include studies involving at least one of each of the populations, interventions, outcomes, and study designs listed below.

Populations

Adults with:

- Acute coronary syndromes
- Recent or ongoing coronary revascularization by stenting or bypass grafting
- Prior ischemic stroke or transient ischemic attack
- Symptomatic peripheral vascular disease

Interventions

- Clopidogrel (Plavix®) alone or in combination with aspirin
- Ticlopidine (Ticlid®) alone or in combination with aspirin
- Dipyridamole (Persantine®, generic brands) in combination with aspirin
- Dipyridamole ER in combination with aspirin (Aggrenox®)

Efficacy and Effectiveness Outcomes

- All-cause mortality
- Cardiovascular mortality
- Myocardial infarction
- Stroke
- Failure of an invasive vascular procedure

Safety Outcomes

- Overall adverse effects
- Withdrawals due to adverse effects
- Serious adverse events, such as neutropenia or major hemorrhage
- Specific adverse events, such as diarrhea or rash
- Withdrawals due to specific adverse events

Study Designs

- Controlled clinical trials
- Systematic reviews
- Observational studies that focused on serious and rare adverse events or that included more than 1,000 patients and had a duration of at least one year

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from March 2008 through May Week 3 2009, using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/index_e.html) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Medline search

Searches resulted in 160 citations. Of those, there are 3 new potentially relevant trials (Table 1) and 5 publications of secondary analyses from previously included trials (Table 2). Appendix A lists the abstracts for these publications. Taken together with the new publications identified in the prior preliminary update scan (Appendix B), now there are a total of 7 new trials and 11 publications of secondary analyses from previously included trials that would likely be added in a full update of this review.

Table 1. New Trials

Study	Population	Comparison	Notes
Diener 2008/Sacco 2008	Ischemic stroke	Dipyridamole ER+aspirin vs clopidogrel	PRoFESS trial: Previously cited as ongoing
Fukuuchi 2008	Japanese patients with noncardioembolic cerebral infarction	Clopidogrel vs ticlopidine	No previous head-to-head trials in the stroke population
Kayacioglu 2008	Revascularization by bypass grafting	Clopidogrel+ASA vs ASA alone	Incidence of graft occlusion

Table 2. Secondary Publications of Previously Included Trials

Author Year	Trial Name and Comparison
<i>CREDO (clopidogrel+aspirin vs aspirin alone in revascularization patients)</i>	
Aronow 2009	Optimal duration
Best 2008	CKD patients
<i>CHARISMA (clopidogrel+aspirin vs aspirin alone in stroke patients)</i>	
Hart 2008	Patients with a history of atrial fibrillation
Mak 2008	Ethnicity
Wang 2007	Primary prevention cohort (asymptomatic with CV risk factors)

Search of FDA and HealthCanada Websites

New Drugs: None

New Indications: None

New Safety Alerts: None

Other considerations

Drugs pending FDA-approval:

1. Prasugrel: NDA for use in ACS was filed in early 2008. FDA decision delayed due to potential increased risk of bleeding in some patient subgroups.
2. Ticagrelor (Brilinta) made by AstraZeneca and may be submitted for FDA-approval late this year. Methods publication available for the PLATO study which is comparing ticagrelor to clopidogrel in ACS patients

Scope issues

This preliminary update scan identified 4 publications (Appendix C) examining different dosage strategies for clopidogrel (e.g., optimal treatment duration, high-dose compared with low-dose). Although not eligible under the current criteria, due to increased clinical relevance, in the event of an update, DERP Participating Organizations may consider revising Key Questions/Inclusion Criteria to encompass these issues.

Table 3. Completed and Ongoing Trials of Different Dosing Strategies for Clopidogrel

Author Year	Population	Notes
<i>Optimal Treatment Duration</i>		
Byrne 2009	Revascularization (drug-eluting stent)	Publication of design and rationale of ISAR-SAFE trial, in which all patients are given clopidogrel for 6 months and then randomized to placebo or 6 more months of clopidogrel.
<i>High-dose compared with low-dose</i>		
Abuzahra 2008	Revascularization (drug-eluting stent)	Results from a trial that compared a high-dose regimen with standard dosing.
Mehta 2008	Acute Coronary Syndromes	Publication of design and rationale for CURRENT-OASIS, which is an ongoing 2x2 factorial trial comparing high-dose to standard dose clopidogrel and high-dose and low-dose ASA.
Price 2009	Revascularization (drug-eluting stent) in patients with high residual platelet reactivity	Publication of design and rationale of the ongoing GRAVITAS trial, which compares high-dose and standard dose clopidogrel.

Additionally, the current report does not include STEMI as a population. We are aware of several studies in this population.

Appendix A. Abstracts of potentially relevant new trials of Newer Antiplatelet Agents for Preliminary Update Scan #2

New trials

Diener, H.-C., R. L. Sacco, et al. (2008). "Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study.[see comment][erratum appears in *Lancet Neurol.* 2008 Nov;7(11):985]." *Lancet Neurology* 7(10): 875-84.

BACKGROUND: The treatment of ischaemic stroke with neuroprotective drugs has been unsuccessful, and whether these compounds can be used to reduce disability after recurrent stroke is unknown. The putative neuroprotective effects of antiplatelet compounds and the angiotensin II receptor antagonist telmisartan were investigated in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial.

METHODS: Patients who had had an ischaemic stroke were randomly assigned in a two by two factorial design to receive either 25 mg aspirin (ASA) and 200 mg extended-release dipyridamole (ER-DP) twice a day or 75 mg clopidogrel once a day, and either 80 mg telmisartan or placebo once per day. The predefined endpoints for this substudy were disability after a recurrent stroke, assessed with the modified Rankin scale (mRS) and Barthel index at 3 months, and cognitive function, assessed with the mini-mental state examination (MMSE) score at 4 weeks after randomisation and at the penultimate visit. Analysis was by intention to treat. The study was registered with ClinicalTrials.gov, number NCT00153062. **FINDINGS:** 20,332 patients (mean age 66 years) were randomised and followed-up for a median of 2.4 years. Recurrent strokes occurred in 916 (9%) patients randomly assigned to ASA with ER-DP and 898 (9%) patients randomly assigned to clopidogrel; 880 (9%) patients randomly assigned to telmisartan and 934 (9%) patients given placebo had recurrent strokes. mRS scores were not statistically different in patients with recurrent stroke who were treated with ASA and ER-DP versus clopidogrel ($p=0.38$), or with telmisartan versus placebo ($p=0.61$). There was no significant difference in the proportion of patients with recurrent stroke with a good outcome, as measured with the Barthel index, across all treatment groups. Additionally, there was no significant difference in the median MMSE scores, the percentage of patients with an MMSE score of 24 points or less, the percentage of patients with a drop in MMSE score of 3 points or more between 1 month and the penultimate visit, and the number of patients with dementia among the treatment groups. There were no significant differences in the proportion of patients with cognitive impairment or dementia among the treatment groups. **INTERPRETATION:** Disability due to recurrent stroke and cognitive decline in patients with ischaemic stroke were not different between the two antiplatelet regimens and were not affected by the preventive use of telmisartan.

Fukuuchi, Y., H. Tohgi, et al. (2008). "A randomized, double-blind study comparing the safety and efficacy of clopidogrel versus ticlopidine in Japanese patients with noncardioembolic cerebral infarction." *Cerebrovascular Diseases* 25(1-2): 40-9.

BACKGROUND: Patients treated with ticlopidine require careful hematologic monitoring. Clopidogrel may have greater tolerability. However, no direct comparison of

these two drugs has been reported and evidence of improved safety with clopidogrel is not yet established in the Japanese population. A comparison of both agents was therefore conducted in Japanese stroke patients. **METHODS:** Patients with noncardioembolic cerebral infarction were randomized to clopidogrel 75 mg or ticlopidine 200 mg once daily for 52 weeks. The primary endpoint was safety; the major secondary endpoint was the incidence of vascular events. **RESULTS:** Clopidogrel was associated with significantly fewer safety events than ticlopidine (7.0 versus 15.1%; $p < 0.001$) and no significant difference in efficacy between the two treatments was seen [hazard ratio 0.977 (95% confidence interval: 0.488-1.957)]. **CONCLUSIONS:** In Japanese stroke patients, clopidogrel 75 mg is better tolerated than ticlopidine 200 mg once daily. Copyright (c) 2007 S. Karger AG, Basel.

Kayacioglu, I., R. Gunay, et al. (2008). "The role of clopidogrel and acetylsalicylic acid in the prevention of early-phase graft occlusion due to reactive thrombocytosis after coronary artery bypass operation." *Heart Surgery Forum* **11**(3): E152-7.

BACKGROUND: Reactive thrombocytosis has been reported in 20% of patients after coronary artery bypass grafting (CABG), a frequency that might be related to the high incidence of thrombotic complications. The present study was planned to investigate the effect of combined treatment with clopidogrel and acetylsalicylic acid (ASA) on post-CABG reactive thrombocytosis. **METHODS:** Included in this prospective, randomized study were 60 patients who underwent CABG operation with a 6-month follow-up. Three study groups were defined: group 1 ($n = 20$), a control group of patients who have not developed reactive thrombocytosis after CABG surgery; group 2 ($n = 20$), patients who have developed reactive thrombocytosis and continue taking ASA (300 mg/day); and group 3 ($n = 20$), patients who have developed reactive thrombocytosis and continue taking ASA (300 mg/day) with the addition of clopidogrel (75 mg/day). **RESULTS:** The mean ages and sex distributions of the patient groups were similar. There were no significant differences between the groups regarding cardiovascular risk factors, baseline laboratory findings, or intraoperative characteristics. Thrombocytosis disappeared within the first month after the operation in both treatment groups. An evaluation of graft patency in the sixth postoperative month revealed that group 2 had significantly more patients with a "positive" result in the exercise test than group 3 and that group 3 had a lower incidence of graft occlusion than group 2 ($P < .01$). **CONCLUSIONS:** Combination antiplatelet therapy with ASA and clopidogrel seems to be more effective than ASA alone for maintaining graft patency in patients with reactive thrombocytosis.

Sacco, R. L., H.-C. Diener, et al. (2008). "Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke.[see comment]." *New England Journal of Medicine* **359**(12): 1238-51.

BACKGROUND: Recurrent stroke is a frequent, disabling event after ischemic stroke. This study compared the efficacy and safety of two antiplatelet regimens--aspirin plus extended-release dipyridamole (ASA-ERDP) versus clopidogrel. **METHODS:** In this double-blind, 2-by-2 factorial trial, we randomly assigned patients to receive 25 mg of aspirin plus 200 mg of extended-release dipyridamole twice daily or to receive 75 mg of clopidogrel daily. The primary outcome was first recurrence of stroke. The secondary outcome was a composite of stroke, myocardial infarction, or death from vascular causes. Sequential statistical testing of noninferiority (margin of 1.075), followed by superiority

testing, was planned. RESULTS: A total of 20,332 patients were followed for a mean of 2.5 years. Recurrent stroke occurred in 916 patients (9.0%) receiving ASA-ERDP and in 898 patients (8.8%) receiving clopidogrel (hazard ratio, 1.01; 95% confidence interval [CI], 0.92 to 1.11). The secondary outcome occurred in 1333 patients (13.1%) in each group (hazard ratio for ASA-ERDP, 0.99; 95% CI, 0.92 to 1.07). There were more major hemorrhagic events among ASA-ERDP recipients (419 [4.1%]) than among clopidogrel recipients (365 [3.6%]) (hazard ratio, 1.15; 95% CI, 1.00 to 1.32), including intracranial hemorrhage (hazard ratio, 1.42; 95% CI, 1.11 to 1.83). The net risk of recurrent stroke or major hemorrhagic event was similar in the two groups (1194 ASA-ERDP recipients [11.7%], vs. 1156 clopidogrel recipients [11.4%]; hazard ratio, 1.03; 95% CI, 0.95 to 1.11). CONCLUSIONS: The trial did not meet the predefined criteria for noninferiority but showed similar rates of recurrent stroke with ASA-ERDP and with clopidogrel. There is no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke. (ClinicalTrials.gov number, NCT00153062.) 2008 Massachusetts Medical Society

Secondary Analysis from Previously Included Trials

Aronow, H. D., S. R. Steinhubl, et al. (2009). "Bleeding risk associated with 1 year of dual antiplatelet therapy after percutaneous coronary intervention: Insights from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial." American Heart Journal **157**(2): 369-74.

BACKGROUND: The optimal duration of dual antiplatelet therapy after percutaneous coronary intervention (PCI) is unknown. Incremental reductions in the risk of major adverse cardiovascular events may be partially offset by an increased incidence of bleeding in the months after a PCI. **METHODS:** We examined the incidence, severity, and predictors of bleeding associated with 1 year of dual antiplatelet therapy after PCI among 1,816 patients in the Clopidogrel for the Reduction of Event During Observation (CREDO) trial. We also compared bleeding in patients who received dual antiplatelet therapy for 1 year to those who did so for only 4 weeks. Bleeding was categorized as major or minor using the modified Thrombolysis In Myocardial Infarction (TIMI) Study Group criteria. **RESULTS:** Major or minor bleeding occurred in 146 patients during 1 year of follow-up. More than 80% of bleeding events were periprocedural. Multivariable predictors of any bleeding included increasing age and coronary artery bypass. Any (major or minor) bleeding occurred in 71 (8.1%) and 77 (8.9%), major bleeding in 34 (3.9%) and 49 (5.6%), and minor bleeding in 37 (4.2%) and 29 (3.3%) of placebo- and clopidogrel-treated patients, respectively; these differences were not significant. However, major gastrointestinal bleeding occurred in significantly more clopidogrel- than placebo-treated patients (13 [1.4%] vs 3 [0.3%] [P = .011]). **CONCLUSIONS:** Adding clopidogrel to aspirin beyond 4 weeks post PCI is not associated with a significant increase in the overall rate of major or minor bleeding, although it is associated with an increase in major gastrointestinal bleeding in the year after a PCI.

Best, P. J. M., S. R. Steinhubl, et al. (2008). "The efficacy and safety of short- and long-term dual antiplatelet therapy in patients with mild or moderate chronic kidney disease: results from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial." American Heart Journal **155**(4): 687-93.

BACKGROUND: Mild and moderate chronic kidney disease (CKD) is associated with decreased survival and increased adverse events after a percutaneous coronary intervention (PCI). Therapy with clopidogrel decreases adverse events in large patient populations. Therefore, we sought to determine the efficacy and safety of long-term clopidogrel therapy in patients with CKD. **METHODS:** Two thousand two patients from the CREDO trial in whom an elective PCI of a single or multiple vessels was planned were analyzed. Patients were randomly assigned to a 300-mg loading dose of clopidogrel before PCI followed by clopidogrel 75 mg/d for a year versus a placebo loading dose at the time of the PCI procedure and clopidogrel 75 mg/d for 28 days and placebo for the remainder of a year. Patients were categorized by their estimated creatinine clearance (>90 [normal, n = 999], 60-89 [mild CKD, n = 672], <60 mL/min [moderate CKD, n = 331]). **RESULTS:** Diminished renal function was associated with worse outcomes. Patients with normal renal function who received 1 year of clopidogrel had a marked reduction in

death, myocardial infarction, or stroke compared with those who received placebo (10.4% vs 4.4%, $P < .001$), whereas patients with mild and moderate CKD did not have a significant difference in outcomes with clopidogrel therapy versus placebo (mild: 12.8% vs 10.3%, $P = .30$; moderate: 13.1% vs 17.8%, $P = .24$). Clopidogrel use was associated with an increased relative risk of major or minor bleeding, but this increased risk was not different based on renal function (relative risk 1.2, 1.3, 1.1). **CONCLUSIONS:** Clopidogrel in mild or moderate CKD patients may not have the same beneficial effect as it does in patients with normal renal function, but was not associated with a greater relative risk of bleeding based on renal function. Further studies are needed to define the role of clopidogrel therapy in patients with CKD.

Hart, R. G., D. L. Bhatt, et al. (2008). "Clopidogrel and aspirin versus aspirin alone for the prevention of stroke in patients with a history of atrial fibrillation: subgroup analysis of the CHARISMA randomized trial." Cerebrovascular Diseases **25**(4): 344-7.

BACKGROUND: Aspirin offers modest reduction in stroke in patients with atrial fibrillation. Whether combination of aspirin with clopidogrel offers additional protection is unclear. **METHODS:** Post-hoc subgroup analysis of 593 participants with a history of atrial fibrillation in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) randomized trial testing clopidogrel 75 mg per day plus aspirin (75-162 mg per day) vs. aspirin alone in patients with stable cardiovascular disease or multiple cardiovascular risk factors. **RESULTS:** Mean patient age was 70 years, 78% were men, and hypertension, heart failure and diabetes were present in 78, 20 and 44%, respectively. During a median follow-up of 2.3 years, stroke (ischemic and hemorrhagic) occurred in 15 of 298 assigned to clopidogrel plus aspirin and in 14 of 285 given aspirin alone (hazard ratio, HR, 1.03, 95% CI 0.49-2.1). There was no difference in all-cause mortality (HR 1.1, 95% CI 0.6-1.9) or in the composite of stroke, myocardial infarction, or vascular death (HR = 1.2, 95% CI 0.7-2.0). Severe/fatal extracranial hemorrhage occurred in 6 patients with combination vs. 3 with aspirin alone. **CONCLUSIONS:** This post-hoc subgroup analysis does not support the use of this combination over aspirin alone in patients with a history of atrial fibrillation pending results of ongoing larger randomized trials. (c) 2008 S. Karger AG, Basel.

Mak, K.-H., D. L. Bhatt, et al. (2009). "Ethnic variation in adverse cardiovascular outcomes and bleeding complications in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study." American Heart Journal **157**(4): 658-65.

BACKGROUND: Atherothrombosis is a common condition affecting individuals worldwide. Its impact on different ethnic groups receiving evidence-based therapy is unclear. We aimed to determine if ethnicity is an independent predictor for cardiovascular events and bleeding complications in a contemporary clinical trial on antiplatelet therapy. **METHODS:** This was a prospective observational study of 15,603 patients enrolled in the CHARISMA trial followed up every 6 months for a median of 28 months. The primary efficacy end point was the first occurrence of cardiovascular death, myocardial infarction, or stroke. The primary safety end point was bleeding. **RESULTS:**

The cohort comprised 12,502 (80.1%) white, 486 (3.1%) black, 775 (5.0%) Asian, and 1,613 (10.3%) Hispanic patients. There was no difference in the occurrence of the primary composite end point among the 4 ethnic groups. Compared with Asians, cardiovascular and all-cause mortality occurred more frequently among black (adjusted hazard 2.19 and 2.04) and Hispanic (adjusted hazard, 1.83 and 1.69) patients. Although the occurrence of severe bleeding was similarly low among the 4 ethnic groups, Asian (adjusted hazard, 2.21) and black (adjusted hazard, 3.06) patients were more likely to have moderate bleeding complications than Hispanic patients. **CONCLUSION:** In this trial of individuals at risk of vascular events, ethnicity was not a significant, independent predictor of the primary composite cardiovascular event. However, ethnicity was a significant, independent predictor of the secondary outcomes, cardiovascular and all-cause mortality (blacks and Hispanics), and moderate bleeding complications (blacks and Asians).

Wang, T. H., D. L. Bhatt, et al. (2007). "An analysis of mortality rates with dual-antiplatelet therapy in the primary prevention population of the CHARISMA trial.[see comment]." European Heart Journal **28**(18): 2200-7.

AIMS: To examine the unanticipated, excess mortality observed in patients randomized to clopidogrel and aspirin vs. aspirin alone in the prespecified 'asymptomatic' subgroup of CHARISMA, we investigated whether dual-antiplatelet therapy may be associated with adverse cardiovascular (CV) events in a primary prevention population. **METHODS AND RESULTS:** Of 15 603 patients enrolled, 3284 were initially categorized as asymptomatic with CV risk factors, but 995 had a prior CV event, leaving 2289 patients to represent the primary prevention cohort. This subset was compared with 13 148 symptomatic patients with established vascular disease and both were evaluated for CV death and bleeding. A multivariate analysis analysed predictors of CV death in this group. No post mortem data were available. Compared with aspirin alone, a significant increase in CV death ($P = 0.01$) was observed in patients receiving dual-antiplatelet therapy in the asymptomatic population. Within the primary prevention cohort, this excess CV death was not significant ($P = 0.07$). Multivariate analysis of the primary prevention group showed a trend towards excess CV death ($P = 0.054$; HR 1.72; CI 0.99-2.97) with dual-antiplatelet therapy (aspirin plus clopidogrel). Other independent predictors of CV death included increasing age, hypertension, atrial fibrillation, and a history of heart failure. There was a non-significant increase in moderate or severe bleeding ($P = 0.218$) with dual-antiplatelet therapy; thus, bleeding was an unlikely explanation for the excess event rate. **CONCLUSION:** These findings do not support the use of dual-antiplatelet therapy with clopidogrel and aspirin in a primary prevention population. In this subgroup analysis, CV death occurred more frequently than anticipated. The cause of this apparent harm is not elucidated, may represent play of chance, but requires further prospective evaluation.

Appendix B. Abstracts of potentially relevant new trials of Newer Antiplatelet Agents from Preliminary Update Scan #1

Bartorelli, A. L., C. Tamburino, et al. (2007). "Comparison of two antiplatelet regimens (aspirin alone versus aspirin + ticlopidine or clopidogrel) after intracoronary implantation of a carbofilm-coated stent." *American Journal of Cardiology* 99(8): 1062-6.

Stent thrombosis (ST) is an infrequent (0.5% to 1.5%) complication of intracoronary stenting, with severe clinical consequences. This multicenter, randomized study evaluated the clinical outcome in 479 patients (598 lesions treated) who underwent elective coronary stenting with a Carbofilm-coated stent (CarboStent) who met prespecified eligibility criteria and were randomly assigned to receive aspirin alone (n = 235) or aspirin plus a thienopyridine antiplatelet regimen (n = 244). Clinical, angiographic, and procedural characteristics were similar between groups. The primary end point was the incidence of 30-day ST; secondary end points included major vascular or bleeding complications within 30 days and death, acute myocardial infarction, and target vessel revascularization at 6 months. ST occurred in 4 patients (1.4%) in the aspirin-only group and in 1 patient (0.3%) in the aspirin-plus-thienopyridine group (relative risk 0.23, 95% confidence interval 0.03 to 2.08, p = NS). After careful review of cases, 89 patients (19%) with protocol deviations were identified. When they were excluded from the analysis, no ST was observed in either group. Secondary end points were reached by 4% of the aspirin-alone group and 8% of the aspirin-plus-thienopyridine group (relative risk 2.35, 95% confidence interval 0.94 to 5.85, p = NS). In conclusion, after optimal intracoronary implantation of the CarboStent, antiplatelet therapy with aspirin alone was safe and provided efficacy comparable to aspirin plus a thienopyridine in the prevention of ST.

Bhatt, D. L., M. D. Flather, et al. (2007). "Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial.[see comment]." *Journal of the American College of Cardiology* 49(19): 1982-8.

OBJECTIVES: The purpose of this study was to determine the possible benefit of dual antiplatelet therapy in patients with prior myocardial infarction (MI), ischemic stroke, or symptomatic peripheral arterial disease (PAD). **BACKGROUND:** Dual antiplatelet therapy with clopidogrel plus aspirin has been validated in the settings of acute coronary syndromes and coronary stenting. The value of this combination was recently evaluated in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, where no statistically significant benefit was found in the overall broad population of stable patients studied. **METHODS:** We identified the subgroup in the CHARISMA trial who were enrolled with documented prior MI, ischemic stroke, or symptomatic PAD. **RESULTS:** A total of 9,478 patients met the inclusion criteria for this analysis. The median duration of follow-up was 27.6 months. The rate of cardiovascular death, MI, or stroke was significantly lower in the clopidogrel plus aspirin arm than in the placebo plus aspirin arm: 7.3% versus 8.8% (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.72 to 0.96, p = 0.01). Additionally, hospitalizations for ischemia were significantly decreased, 11.4% versus 13.2% (HR 0.86, 95% CI 0.76 to 0.96, p = 0.008). There was no significant difference in the rate of severe bleeding: 1.7% versus 1.5% (HR 1.12, 95% CI 0.81 to 1.53, p = 0.50); moderate bleeding was significantly increased: 2.0% versus 1.3% (HR 1.60, 95% CI 1.16

to 2.20, $p = 0.004$). **CONCLUSIONS:** In this analysis of the CHARISMA trial, the large number of patients with documented prior MI, ischemic stroke, or symptomatic PAD appeared to derive significant benefit from dual antiplatelet therapy with clopidogrel plus aspirin. Such patients may benefit from intensification of antithrombotic therapy beyond aspirin alone, a concept that future trials will need to validate. (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance [CHARISMA]; <http://clinicaltrials.gov/ct/show/NCT00050817?order=1>; NCT00050817).

Brener, S. J., S. R. Steinhubl, et al. (2007). "Prolonged dual antiplatelet therapy after percutaneous coronary intervention reduces ischemic events without affecting the need for repeat revascularization: insights from the CREDO trial." *Journal of Invasive Cardiology* 19(7): 287-90.

BACKGROUND: Dual antiplatelet therapy reduces ischemic events after percutaneous coronary intervention (PCI) and in patients with acute coronary syndromes. The relationship between target vessel revascularization (TVR) and ischemic events in patients treated with aspirin and clopidogrel or aspirin alone from 1 month to 1 year after PCI has not been studied. **METHODS:** Patients enrolled in the CREDO trial were treated with aspirin and clopidogrel or aspirin and placebo for up to 1 year. We compared the rates of TVR and ischemic events (cardiac death, myocardial infarction or stroke) in the two groups, and modeled the effect of clopidogrel treatment on ischemic events after adjusting for relevant parameters. **RESULTS** One month after PCI, 1,955 patients have remained asymptomatic. By 1 year, ischemic events occurred in 5.3% of placebo- and 3.1% of clopidogrel-treated patients; $p = 0.02$. The rate of TVR was 11.9% and 12.2%, respectively; $p = 0.82$. Only 7 patients (clopidogrel: 3 and placebo: 4) experienced TVR within 7 days of an ischemic event. After adjustment, long-term dual antiplatelet therapy was associated with a 48% reduction in events; $p = 0.01$. Patients who experienced TVR had a significantly higher rate of ischemic events than those without TVR, regardless of treatment assignment: 12.3% vs. 3.1%, respectively; $p < 0.001$. **CONCLUSION:** Thus, after successful PCI, prolonged dual antiplatelet therapy reduces ischemic events without affecting TVR. Overall, patients with TVR experienced an ischemic event much more often that was not related to the PCI vessel. This suggests that the benefit of antiplatelet therapy after coronary revascularization is indexed to the patient's underlying atherothrombotic process, rather than the artery that underwent intervention.

Chairangarit, P., P. Sithinamsuwan, et al. (2005). "Comparison between aspirin combined with dipyridamole versus aspirin alone within 48 hours after ischemic stroke event for prevention of recurrent stroke and improvement of neurological function: a preliminary study." *Journal of the Medical Association of Thailand* 88 Suppl 3: S148-54.

OBJECTIVES: To determine efficacy and tolerability of aspirin plus dipyridamole (combination) versus aspirin alone in acute intervention treatment after acute ischemic stroke among Thai patients. **MATERIAL AND METHOD:** This pilot study enrolled ischemic stroke patients within 48 hours and randomized to aspirin 300 mg/d or combination (aspirin 300 mg/d+ standard release dipyridamole 75 mg thrice a day) and followed up for 6 months. Endpoints were recurrent ischemic stroke, transient ischemic attack and vascular death. Side effects were recorded. National Institutes of Health Stroke Scale was assessed at entry and at 6 months period for determining neurological functions. **RESULTS:** Of 38 patients, mean age was 64.3 years. Male and female were 52.6% and 47.4% respectively. There were 18 patients in the aspirin group and 20

patients in the combination group. No patient developed end point events or no significant adverse event in both groups. The combination group showed more improvement in neurological function than the aspirin group (p-value 0.009).
CONCLUSION: This pilot study showed equal efficacy and tolerability of the combination group and aspirin alone in acute intervention treatment for prevention of recurrent stroke or vascular death within 6 months.

Dalainas, I., G. Nano, et al. (2006). "Dual antiplatelet regime versus acetyl-acetic acid for carotid artery stenting." *Cardiovascular & Interventional Radiology* 29(4): 519-21.

Carotid artery stenting has been proposed as an option treatment of carotid artery stenosis. The aim of this single-institution study is to compare the dual-antiplatelet treatment and heparin combined with acetyl-acetic acid, in patients who underwent carotid artery stenting. We compared 2 groups of 50 patents each who underwent carotid artery stenting for primary atherosclerotic disease. Group A received heparin for 24 h combined with 325 mg acetyl-acetic acid and group B received 250 mg ticlopidine twice a day combined with 325 mg acetyl-acetic acid. Outcome measurements included 30-day bleeding and neurological complications and 30-day thrombosis/occlusion rates. The neurological complications were 16% in group A and 2% in group B ($p < 0.05$). Bleeding complications occurred in 4% in group A and 2% in group B ($p > 0.05$). The 30-day thrombosis/occlusion rate was 2% in group A and 0% in group B ($p > 0.05$). Dual antiplatelet treatment is recommended in all patients undergoing carotid artery stenting.

Group, E. S., P. H. A. Halkes, et al. (2006). "Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial.[see comment][erratum appears in *Lancet*. 2007 Jan 27;369(9558):274]." *Lancet* 367(9523): 1665-73.

BACKGROUND: Results of trials of aspirin and dipyridamole combined versus aspirin alone for the secondary prevention of vascular events after ischaemic stroke of presumed arterial origin are inconsistent. Our aim was to resolve this uncertainty. **METHODS:** We did a randomised controlled trial in which we assigned patients to aspirin (30-325 mg daily) with ($n=1363$) or without ($n=1376$) dipyridamole (200 mg twice daily) within 6 months of a transient ischaemic attack or minor stroke of presumed arterial origin. Our primary outcome event was the composite of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication, whichever happened first. Treatment was open, but auditing of outcome events was blinded. Primary analysis was by intention to treat. This study is registered as an International Standard Randomised Controlled Trial (number ISRCTN73824458) and with (NCT00161070). **FINDINGS:** Mean follow-up was 3.5 years (SD 2.0). Median aspirin dose was 75 mg in both treatment groups (range 30-325); extended-release dipyridamole was used by 83% ($n=1131$) of patients on the combination regimen. Primary outcome events arose in 173 (13%) patients on aspirin and dipyridamole and in 216 (16%) on aspirin alone (hazard ratio 0.80, 95% CI 0.66-0.98; absolute risk reduction 1.0% per year, 95% CI 0.1-1.8). Addition of the ESPRIT data to the meta-analysis of previous trials resulted in an overall risk ratio for the composite of vascular death, stroke, or myocardial infarction of 0.82 (95% CI 0.74-0.91). Patients on aspirin and dipyridamole discontinued trial medication more often than those on aspirin alone (470 vs 184), mainly because of headache. **INTERPRETATION:** The ESPRIT results, combined with the results of previous trials, provide sufficient evidence to prefer the combination regimen of aspirin plus

dipyridamole over aspirin alone as antithrombotic therapy after cerebral ischaemia of arterial origin.

Kelly, R. V., A. Hsu, et al. (2006). "The influence of body mass index on outcomes and the benefit of antiplatelet therapy following percutaneous coronary intervention." *Journal of Invasive Cardiology* 18(3): 115-9.

In general, obesity is associated with better outcome in patients undergoing percutaneous coronary interventions (PCI). One small study has suggested that these patients do not achieve adequate platelet inhibition with clopidogrel and that this may shape clinical outcomes. We evaluated the relationship between body mass index (BMI) and clinical outcomes at 1 year following PCI in patients randomized to clopidogrel or placebo in the CREDO trial. **METHODS AND RESULTS:** BMI, baseline clinical characteristics and clopidogrel regimen were assessed in 2,116 patients. The primary study endpoint was the 1-year composite of death, MI or stroke. A total of 342 patients had low or normal BMI (< 25 kg per m²), 847 were overweight (25-29.9 kg per m²), 810 were obese (30-39.9 kg per m²) and 113 were very obese (greater than or equal to 40 kg per m²). Obese patients were more likely to be young males with diabetes, hypertension and hyperlipidemia ($p < 0.01$). Bleeding complications occurred in 38% of low BMI, 32% of overweight/obese, and 25% of very obese patients ($p = 0.03$). Randomization to clopidogrel was associated with a 25% risk reduction in 1-year death, MI or stroke events, as BMI increased by every 5 kg per m² ($p = 0.009$). **CONCLUSION:** In general, increasing BMI was associated with better efficacy and bleeding outcomes at 1 year in this nonurgent PCI population. Randomization to early- and long-term clopidogrel was associated with even further improvements in those with increasing BMI.

Keltai, M., M. Tonelli, et al. (2007). "Renal function and outcomes in acute coronary syndrome: impact of clopidogrel." *European Journal of Cardiovascular Prevention & Rehabilitation* 14(2): 312-8.

INTRODUCTION: Patients with renal dysfunction are more prone to bleeding when receiving antithrombotic drugs. The aim of the study was to assess the impact of clopidogrel on safety and efficacy in patients with renal dysfunction in non-ST elevation acute coronary syndromes. **METHODS AND RESULTS:** Patients in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial were analysed to assess the relationship of chronic kidney disease to cardiovascular outcomes. Renal function was estimated by the glomerular filtration rate computed from the baseline serum creatinine measurements in 12 253 (97.5%) patients enrolled in the trial. Patients were grouped into tertiles of glomerular filtration rate. The primary outcome (cardiovascular death, myocardial infarction, stroke combined) occurred more frequently in the lowest glomerular filtration rate tertile. The bleeding risk was also significantly increased in patients in this tertile, compared with the other two. The beneficial effect of adding clopidogrel to standard treatment in non-ST elevation acute coronary syndrome was observed in all three tertiles of renal function {(lower third relative risk (RR)=0.89 [95% confidence interval (CI) 0.76-1.05]; medium third RR=0.68 (95% CI 0.56-0.84); upper third RR=0.74 (95% CI 0.60-0.93) (P for heterogeneity=0.11)}. Clopidogrel treatment significantly increased the risk of minor bleeding in all tertiles of renal function. The risk of major or life-threatening bleeding increased moderately with the addition of clopidogrel to standard treatment [lower third RR=1.12 (95% CI 0.83-1.51); medium

third RR=1.4 (95% CI 0.97-2.02); upper third RR=1.83 (95% CI 1.23-2.73)], but this did not appear to be greatest in those with the lowest renal function. CONCLUSIONS: Even mild chronic kidney disease worsens the prognosis in patients with non-ST elevation acute coronary syndromes. Clopidogrel was beneficial and safe in patients with and without chronic kidney disease.

Kennedy, J., M. D. Hill, et al. (2007). "Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial.[see comment]." *Lancet Neurology* 6(11): 961-9.

BACKGROUND: Patients with transient ischaemic attack (TIA) or minor stroke are at high immediate risk of stroke. The optimum early treatment options for these patients are not known. **METHODS:** Within 24 h of symptom onset, we randomly assigned, in a factorial design, 392 patients with TIA or minor stroke to clopidogrel (300 mg loading dose then 75 mg daily; 198 patients) or placebo (194 patients), and simvastatin (40 mg daily; 199 patients) or placebo (193 patients). All patients were also given aspirin and were followed for 90 days. Descriptive analyses were done by intention to treat. The primary outcome was total stroke (ischaemic and haemorrhagic) within 90 days. Safety outcomes included haemorrhage related to clopidogrel and myositis related to simvastatin. This study is registered as an International Standard Randomised Controlled Trial (number 35624812) and with ClinicalTrials.gov (NCT00109382). **FINDINGS:** The median time to stroke outcome was 1 day (range 0-62 days). The trial was stopped early due to a failure to recruit patients at the prespecified minimum enrolment rate because of increased use of statins. 14 (7.1%) patients on clopidogrel had a stroke within 90 days compared with 21 (10.8%) patients on placebo (risk ratio 0.7 [95% CI 0.3-1.2]; absolute risk reduction -3.8% [95% CI -9.4 to 1.9]; p=0.19). 21 (10.6%) patients on simvastatin had a stroke within 90 days compared with 14 (7.3%) patients on placebo (risk ratio 1.3 [0.7-2.4]; absolute risk increase 3.3% [-2.3 to 8.9]; p=0.25). The interaction between clopidogrel and simvastatin was not significant (p=0.64). Two patients on clopidogrel had intracranial haemorrhage compared with none on placebo (absolute risk increase 1.0% [-0.4 to 2.4]; p=0.5). There was no difference between groups for the simvastatin safety outcomes. **INTERPRETATION:** Immediately after TIA or minor stroke, patients are at high risk of stroke, which might be reduced by using clopidogrel in addition to aspirin. The haemorrhagic risks of the combination of aspirin and clopidogrel do not seem to offset this potential benefit. We were unable to provide evidence of benefit of simvastatin in this setting. This aggressive prevention approach merits further study.

Steinhubl, S. R., P. B. Berger, et al. (2006). "Optimal timing for the initiation of pre-treatment with 300 mg clopidogrel before percutaneous coronary intervention." *Journal of the American College of Cardiology* 47(5): 939-43.

OBJECTIVES: This study sought to determine the optimal timing of a 300-mg clopidogrel loading dose before percutaneous coronary intervention (PCI) in patients enrolled in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. **BACKGROUND:** A loading dose of clopidogrel before a PCI has become relatively commonplace, although the data supporting this practice are limited and sometimes conflicting. **METHODS:** Patients were randomized to receive either 300 mg clopidogrel or a matching placebo administered a minimum of 3 h and a maximum of 24 h before PCI. The primary 28-day combined end point was death, myocardial infarction, or urgent

target vessel revascularization. Linear splines were used to summarize the effect of the time of pre-treatment as a continuous variable. **RESULTS:** A total of 1,762 patients were evaluated. For patients randomized to placebo, there was no relationship between the duration of pre-treatment and the occurrence of the primary end point, whereas longer durations of pre-treatment in patients randomized to clopidogrel were associated with improved outcomes. The event rates diverged maximally at 24 h. The difference in outcomes between placebo and clopidogrel pre-treated patients was not significant until $>$ or $=15$ h pre-treatment, with a 58.8% ($p = 0.028$) reduction in the primary end point in patients pre-treated with clopidogrel $>$ or $=15$ h compared with placebo.

CONCLUSIONS: When a 300-mg loading dose of clopidogrel is used, little benefit is obtained compared with just 75 mg at the time of the PCI when the treatment duration is <12 h. In patients pre-treated for longer durations, the optimal duration seems to approach 24 h.

Appendix C. Abstracts of Clopidogrel Dosing Optimization Studies

Abuzahra, M., M. Pillai, et al. (2008). "Comparison of higher clopidogrel loading and maintenance dose to standard dose on platelet function and outcomes after percutaneous coronary intervention using drug-eluting stents." American Journal of Cardiology **102**(4): 401-3.

Adequate antiplatelet therapy is paramount for good clinical outcomes in patients undergoing percutaneous coronary intervention (PCI). The purpose of this study was to determine whether a high-dose regimen of clopidogrel in patients undergoing PCI is superior to standard dosing. A total of 119 patients undergoing PCI were blindly randomized in 2:1 fashion to receive clopidogrel loading 600 mg on the table immediately before PCI and 75 mg 2 times/day for 1 month (high-dose group) versus standard dosing (300 mg loading and 75 mg/day; low-dose group). Platelet aggregation was measured using light transmission aggregometry at baseline, 4 hours, and 30 days. The composite of cardiovascular death, myocardial infarction, and target vessel revascularization was studied at 30 days in addition to major and minor bleeding. Baseline characteristics and baseline platelet aggregation were similar in the 2 groups. Percent inhibitions of platelet activity were 41% and 27% in the high-dose group versus 19% and 10% in the low-dose group at 4 hours and 30 days ($p = 0.046$ and 0.047 , respectively). Composite clinical end points were 10.3% in the high-dose group and 23.8% in the low-dose group ($p = 0.04$). No difference was noted in major or minor bleeding. In conclusion, a higher loading and maintenance dose of clopidogrel in patients undergoing PCI results in superior platelet inhibition and decreased cardiovascular events without increasing bleeding complications.

Byrne, R. A., S. Schulz, et al. (2009). "Rationale and design of a randomized, double-blind, placebo-controlled trial of 6 versus 12 months clopidogrel therapy after implantation of a drug-eluting stent: The Intracoronary Stenting and Antithrombotic Regimen: Safety And Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) study." American Heart Journal **157**(4): 620-4.e2.

BACKGROUND: Concern regarding the rate of delayed acute stent thrombosis associated with drug-eluting stent (DES) treatment has resulted in upward revision of the advised duration of dual antiplatelet therapy after DES implantation by both European and United States guideline writing committees. In fact, the corroboration of an increased rate of late thrombotic events remains outstanding, and these clinical practice guidelines are limited by an inadequate evidence base on which to ground their recommendations. **HYPOTHESIS:** We postulate that a 6-month duration of clopidogrel therapy after DES implantation is associated with a clinical outcome that is not inferior to that of a 12-month therapy. **STUDY DESIGN:** The Intracoronary Stenting and Antithrombotic Regimen: Safety And Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) is a multinational, double-blind, placebo-controlled, randomized trial designed to examine the effects of a 6-month duration of clopidogrel therapy after DES implantation compared to that of 12 months. Patients on clopidogrel therapy at 6 months after DES implantation will be randomized in a 1:1 fashion to discontinuation of clopidogrel versus a further 6 months of treatment. The

primary end point is a composite of death, myocardial infarction, stent thrombosis, stroke, or thrombolysis in myocardial infarction major bleeding. Clinical follow-up is scheduled at 9 months postrandomization (15 months postintervention). According to power calculations based on a noninferiority design, it is estimated that 6,000 patients are required to be enrolled. SUMMARY: There is clinical equipoise on the issue of optimal duration of dual antiplatelet treatment after percutaneous intervention with DES. The ISAR-SAFE trial aims to assess whether discontinuation of clopidogrel 6 months after DES implantation is noninferior to routine prolongation of such therapy out to 1 year.

Mehta, S. R., J.-P. Bassand, et al. (2008). "Design and rationale of CURRENT-OASIS 7: a randomized, 2 x 2 factorial trial evaluating optimal dosing strategies for clopidogrel and aspirin in patients with ST and non-ST-elevation acute coronary syndromes managed with an early invasive strategy." American Heart Journal **156**(6): 1080-1088.e1.

BACKGROUND: Antiplatelet therapy with clopidogrel and acetylsalicylic acid (ASA) reduces major cardiovascular events in patients with ST and non-ST-segment-elevation acute coronary syndromes (ACS). Recent mechanistic and clinical data suggest that higher loading and maintenance doses of clopidogrel may achieve a more rapid and greater degree of platelet inhibition that translates into improved clinical outcomes, but this is yet to be formally evaluated in an adequately powered randomized trial.

OBJECTIVES: To evaluate the efficacy and safety of (1) a higher loading and initial maintenance dose of clopidogrel compared with the standard-dose regimen and (2) high-dose ASA compared with low-dose ASA in patients with ST or non-ST-segment-elevation ACS managed with an early invasive strategy. DESIGN: Multicenter, international, randomized, 2 x 2 factorial design trial evaluating a clopidogrel high-dose regimen (600 mg loading dose on day 1 followed by 150 mg once daily on days 2 to 7, followed by 75 mg once daily on days 8-30) compared with the standard-dose regimen (300 mg loading dose on day 1, followed by 75 mg once daily on days 2-30) and high-dose ASA (300-325 mg daily) versus low-dose ASA (75-100 mg daily) in patients with ST or non-ST-segment-elevation ACS managed with an early invasive strategy. The clopidogrel dose comparison is double-blind and the ASA dose comparison is open-label. The primary outcome is the composite of death from cardiovascular causes, myocardial (re)infarction or stroke up to day 30. The primary safety outcome is major bleeding. The sample size is 18,000 to 20,000 patients. CONCLUSIONS: The CURRENT-OASIS 7 trial will help to define optimal dosing regimens for clopidogrel and ASA in patients with ST and non-ST-segment-elevation ACS treated with an early invasive strategy.

Price, M. J., P. B. Berger, et al. (2009). "Evaluation of individualized clopidogrel therapy after drug-eluting stent implantation in patients with high residual platelet reactivity: design and rationale of the GRAVITAS trial." American Heart Journal **157**(5): 818-24.

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.