

Drug Class Review on Newer Antiplatelet Agents

Update #2: Preliminary Scan Report

March 2008

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.

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director
Marian S McDonagh, Principal Investigator,
Drug Effectiveness Review Project

Update scan prepared by Susan Severance, MPH



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)

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 May 2006 through March Week 2, 2008, 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

Overview

Searches resulted in 94 citations. Of those, there are 10 new potentially relevant trials (see Appendix A, attached).

Study	Notes
Bartorelli 2007	Aspirin alone vs aspirin + ticlopidine or clopidogrel
Bhatt 2007	Secondary CHARISMA trial study
Brener 2007	Secondary CREDO trial study
Chairangsarit 2005	Aspirin alone vs aspirin + dipyridamole
Dalainas 2006	Acetyl-acetic acid vs acetyl-acetic acid + ticlopidine
Group 2006	Secondary ESPRIT trial study
Kelly 2006	Secondary CREDO trial study, influence of BMI
Keltai 2007	Secondary CURE trial study
Kennedy 2007	Clopidogrel vs placebo (FASTER trial)
Steinhubl 2006	Secondary CREDO trial study

New Drugs

No new drugs were identified.

New Indications

A new indication for Plavix from 8/17/2006 was identified.

The supplemental new drug application provides for the following new use of Plavix (clopidogrel bisulfate) 75 mg tablets: For patients with ST-segment elevation acute myocardial infarction, Plavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke. This benefit is not known to pertain to patients who receive primary angioplasty.

New Safety Alerts

New information was added to the product safety labels for 2 newer antiplatelet agents. Details of these changes are listed in the table below.

Newer Antiplatelet Agent	Date of change	Details of new safety information
clopidogrel	8/06	Label Change: Warnings, Precautions and Adverse Reactions
		<p>WARNINGS: Thrombotic thrombocytopenic purpura (TTP). TTP has been reported rarely following use of Plavix, sometimes after a short exposure (< 2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever.</p>
clopidogrel	8/06	Label Change: Precautions and Adverse Reactions
		<p>PRECAUTIONS: Drug Interactions: Thrombolytics; Oral Anticoagulants. Geriatric Use. ADVERSE REACTIONS: Gastrointestinal System Disorders; Peptic, gastric or duodenal ulcer; Gastritis. White Cell and Reticuloendothelial System Disorders; Neutropenia</p>
Aspirin/Dipyridamole	11/06	Label Change:
		<p>Adverse Reactions</p> <p>Aggrenox</p> <p>Other adverse reactions:Skin and appendages disorders: Pruritus;urticaria</p>
Aspirin/Dipyridamole	3/07	Label Change:
		<p>Adverse Reactions</p> <p>Aggrenox</p> <p>Adverse Reactions: Headache was most notable in the first month of treatment.</p>
clopidogrel	5/07	Label change:
		<p>warnings & precautions</p> <p>Plavix (clopidogrel bisulfate tablets)</p> <p>WARNINGS: Thrombotic Thrombocytopenic Purpura (TTP) TTP has been reported rarely following use of Plavix, sometimes after a short exposure (<2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever.</p>

Newer Antiplatelet Agent	Date of change	Details of new safety information
		<p>PRECAUTIONS</p> <p>Information for Patients</p> <p>Patients should be told that it may take them longer than usual to stop bleeding, that they may bruise and/or bleed more easily when they take Plavix or Plavix combined with aspirin, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking Plavix and/or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken.</p>

Appendix A. Abstracts of potentially relevant new trials of Newer Antiplatelet Agents

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.