

Drug Class Review on Newer Antiplatelet Agents

Update #2: Preliminary Scan Report #3

April 2010

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

Preliminary Update Scan #2: June 2009

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 from May 2009 to April Week 2, 2010, using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. For the new drug prasugrel (Effient®) we searched from 1948 to April Week 2, 2010 by using the same search terms. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (<http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/index-eng.php>) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote XI) 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

New FDA –approved Drug

Prasugrel (Effient®) approved on July 10, 2009 and available as EQ 5 mg and 10 mg base in U.S. market

New Indications

None

New Safety Alerts

Our review of the FDA's MedWatch website identified the following new safety information for clopidogrel:

As of March of 2010, the following black box warning was added to the product label for clopidogrel:

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see Warnings and Precautions (5.1)]. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype;

these tests can be used as an aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers

Also for clopidogrel in March of 2010, information was added to the ‘Warnings and Precautions’ section of the product label regarding the risk of diminished antiplatelet activity with concomitant use of drugs that inhibit CYP2C19 activity, such as omeprazole, the general risk of bleeding following surgery, and the risk of cardiovascular events associated with premature discontinuation of clopidogrel.

August 2009: Our review of the Health Canada website found similar information regarding the potential for decreased effects of clopidogrel when taken with proton pump inhibitors.

Medline search

Searches resulted in 162 citations. Of those, there are 4 new potentially relevant trials and 8 publications of secondary analyses from published trials (Table 1). Appendix A lists the abstracts for these publications. Taken together with the new publications identified in the prior preliminary update scans (Appendix B), now there are a total of 11 new trials and 19 publications of secondary analyses of published trials that would likely be added in a full update of this review.

Table 1. New Trials

Study	Population	Comparison
Primary publications		
Dengler EARLY Trial	Ischemic stroke	Aspirin+ER dipyridamole vs aspirin
Uchiyama, 2009	Japanese stroke patients	Clopidogrel vs ticlopidine
Wiviott, 2005 JUMBO-TIMI 26	Patients undergoing percutaneous coronary intervention	Prasugrel vs clopidogrel
Wiviott, 2007 TRITON-TIMI 38	Acute coronary syndromes with scheduled percutaneous coronary intervention	Prasugrel vs clopidogrel
Secondary publications		
TRITON-TIMI 38 secondary publications (Prasugrel vs Clopidogrel)		
Morrow, 2009	Myocardial infarction patients	
O'Donoghue, 2009	Prasugrel vs clopidogrel with or without a glycoprotein IIb/IIIa inhibitor	
Pride, 2009	Patients undergoing percutaneous coronary intervention without stent implantation	
Wiviott, 2007	Design and rationale of the trial	
CHARISMA (clopidogrel+aspirin vs aspirin alone)		
Berger 2009	All cause, cardiovascular, cancer mortality	
Cacoub, 2009	Major cardiovascular events	
Collet, 2009	Clinical outcomes following discontinuation	
Dasgupta, 2009	Diabetic nephropathy patients	

Appendix A. Abstracts of potentially new trials of Newer Antiplatelet Agents for Preliminary Update Scan #3

New Trials

Dengler, R., H.-C. Diener, et al. "Early treatment with aspirin plus extended-release dipyridamole for transient ischaemic attack or ischaemic stroke within 24 h of symptom onset (EARLY trial): a randomised, open-label, blinded-endpoint trial." *Lancet Neurology* **9**(2): 159-66.

BACKGROUND: Little is known about the best antiplatelet treatment immediately after ischaemic stroke or transient ischaemic attack (TIA). The EARLY trial aimed to compare outcome in patients given aspirin plus extended-release dipyridamole twice daily either within 24 h of stroke or TIA or after 7 days of aspirin monotherapy. **METHODS:** In 46 stroke units in Germany, patients aged 18 years or more who presented with symptoms of an acute ischaemic stroke that caused a measurable neurological deficit (National Institutes of Health stroke scale score < or =20) were randomly assigned to receive 25 mg aspirin plus 200 mg extended-release dipyridamole open-label twice daily or 100 mg aspirin monotherapy open-label once daily for 7 days. Patients were randomised by use of a pseudorandom number generator. All patients were then given open-label aspirin plus extended-release dipyridamole for up to 90 days. The primary endpoint was modified Rankin scale score as recorded by centralised, blinded assessment by telephone (tele-mRS) at 90 days. Vascular adverse events (non-fatal stroke, TIA, non-fatal myocardial infarction, and major bleeding complications) and mortality were assessed in a composite safety and efficacy endpoint. Patients were analysed as treated. This trial is registered, number NCT00562588. **FINDINGS:** Between July, 2007, and February, 2009, 543 patients were treated: 283 received early aspirin plus extended-release dipyridamole and 260 received aspirin plus extended-release dipyridamole after 7 days on aspirin. At day 90, 154 (56%) patients in the aspirin plus early extended-release dipyridamole group and 133 (52%) in the aspirin plus later extended-release dipyridamole group had no or mild disability (tele-mRS 0 or 1; difference 4.1%, 95% CI -4.5 to 12.6, p=0.45). 28 patients in the early initiation group and 38 in the late initiation group reached the composite endpoint (hazard ratio 0.73, 95% CI 0.44-1.19 p=0.20). **INTERPRETATION:** Early initiation of aspirin plus extended-release dipyridamole within 24 h of stroke onset is likely to be as safe and effective in preventing disability as is later initiation after 7 days. **FUNDING:** Boehringer Ingelheim. Copyright (c) 2010 Elsevier Ltd. All rights reserved.

Uchiyama, S., Y. Fukuuchi, et al. (2009). "The safety and efficacy of clopidogrel versus ticlopidine in Japanese stroke patients: combined results of two Phase III, multicenter, randomized clinical trials." *Journal of Neurology* **256**(6): 888-97.

Two Phase III studies comparing the safety and efficacy of clopidogrel with ticlopidine as antiplatelet agents for the secondary prevention of vascular events in patients with prior stroke were performed in Japan. Both studies were randomized, double-blind, double-dummy comparative trials with the primary objective of comparing the clinical safety of

treatment with either clopidogrel or ticlopidine for up to 12 months. The secondary objective was to assess the incidence of a combined efficacy endpoint of cerebral infarction, myocardial infarction, and vascular death. Patients with prior stroke were recruited during July 1996-February 1998 and September 2001-November 2003 at centers across Japan. The results of the two studies were combined in this analysis. There were 1,869 patients in the safety population (clopidogrel, 941; ticlopidine, 928). Significantly, fewer patients experienced a safety event in the clopidogrel group than in the ticlopidine group ($p < 0.001$; hazard ratio, 0.610; 95% confidence interval 0.529, 0.703). Almost twice as many patients in the ticlopidine group (25.6%) experienced hepatic dysfunction than in the clopidogrel group (13.4%). There were 1,862 patients evaluable for efficacy (clopidogrel, 939; ticlopidine, 923). There was no significant difference in the incidence of the combined efficacy endpoint between clopidogrel (2.6% of patients) and ticlopidine (2.5%). Clopidogrel was better tolerated than ticlopidine. There was no difference in the efficacy of the two agents with regard to the secondary prevention of vascular events in patients with prior stroke. This was the first combined analysis of direct comparison of clopidogrel with ticlopidine in the clinical setting.

Wiviott, S. D., E. M. Antman, et al. (2005). "Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y₁₂ antagonist, with clopidogrel in percutaneous coronary intervention: results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 trial." *Circulation* **111**(25): 3366-73.

BACKGROUND: Despite the current standard antiplatelet regimen of aspirin and clopidogrel (with or without glycoprotein IIb/IIIa inhibitors) in percutaneous coronary intervention patients, periprocedural and postprocedural ischemic events continue to occur. Prasugrel (CS-747, LY640315), a novel potent thienopyridine P2Y₁₂ receptor antagonist, has the potential to achieve higher levels of inhibition of ADP-induced platelet aggregation than currently approved doses of clopidogrel. **METHODS AND RESULTS:** Joint Utilization of Medications to Block Platelets Optimally-Thrombolysis In Myocardial Infarction 26 (JUMBO-TIMI 26) was a phase 2, randomized, dose-ranging, double-blind safety trial of prasugrel versus clopidogrel in 904 patients undergoing elective or urgent percutaneous coronary intervention. Patients were randomized to either standard dosing with clopidogrel or 1 of 3 prasugrel regimens. Subjects were monitored for 30 days for bleeding and clinical events. The primary end point of the trial was clinically significant (TIMI major plus minor) non-CABG-related bleeding events in prasugrel- versus clopidogrel-treated patients. Hemorrhagic complications were infrequent, with no significant difference between patients treated with prasugrel or clopidogrel in the rate of significant bleeding (1.7% versus 1.2%; hazard ratio, 1.42; 95% CI, 0.40, 5.08). In prasugrel-treated patients, there were numerically lower incidences of the primary efficacy composite end point (30-day major adverse cardiac events) and of the secondary end points myocardial infarction, recurrent ischemia, and clinical target vessel thrombosis. **CONCLUSIONS:** In this phase 2 study, which was designed to assess safety when administered at the time of percutaneous coronary intervention, prasugrel and clopidogrel both resulted in low rates of bleeding. The results of this trial serve as a

foundation for the large phase 3 clinical trial designed to assess both efficacy and safety.

Wiviott, S. D., E. Braunwald, et al. (2007). "Prasugrel versus clopidogrel in patients with acute coronary syndromes." New England Journal of Medicine **357**(20): 2001-15.

BACKGROUND: Dual-antiplatelet therapy with aspirin and a thienopyridine is a cornerstone of treatment to prevent thrombotic complications of acute coronary syndromes and percutaneous coronary intervention. **METHODS:** To compare prasugrel, a new thienopyridine, with clopidogrel, we randomly assigned 13,608 patients with moderate-to-high-risk acute coronary syndromes with scheduled percutaneous coronary intervention to receive prasugrel (a 60-mg loading dose and a 10-mg daily maintenance dose) or clopidogrel (a 300-mg loading dose and a 75-mg daily maintenance dose), for 6 to 15 months. The primary efficacy end point was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The key safety end point was major bleeding. **RESULTS:** The primary efficacy end point occurred in 12.1% of patients receiving clopidogrel and 9.9% of patients receiving prasugrel (hazard ratio for prasugrel vs. clopidogrel, 0.81; 95% confidence interval [CI], 0.73 to 0.90; $P < 0.001$). We also found significant reductions in the prasugrel group in the rates of myocardial infarction (9.7% for clopidogrel vs. 7.4% for prasugrel; $P < 0.001$), urgent target-vessel revascularization (3.7% vs. 2.5%; $P < 0.001$), and stent thrombosis (2.4% vs. 1.1%; $P < 0.001$). Major bleeding was observed in 2.4% of patients receiving prasugrel and in 1.8% of patients receiving clopidogrel (hazard ratio, 1.32; 95% CI, 1.03 to 1.68; $P = 0.03$). Also greater in the prasugrel group was the rate of life-threatening bleeding (1.4% vs. 0.9%; $P = 0.01$), including nonfatal bleeding (1.1% vs. 0.9%; hazard ratio, 1.25; $P = 0.23$) and fatal bleeding (0.4% vs. 0.1%; $P = 0.002$). **CONCLUSIONS:** In patients with acute coronary syndromes with scheduled percutaneous coronary intervention, prasugrel therapy was associated with significantly reduced rates of ischemic events, including stent thrombosis, but with an increased risk of major bleeding, including fatal bleeding. Overall mortality did not differ significantly between treatment groups. (ClinicalTrials.gov number, NCT00097591 [ClinicalTrials.gov].) Copyright 2007 Massachusetts Medical Society.

Secondary analysis of published trials

Berger, J. S., D. L. Bhatt, et al. (2009). "Smoking, clopidogrel, and mortality in patients with established cardiovascular disease." Circulation **120**(23): 2337-44.

BACKGROUND: Smoking increases platelet aggregability and the degree of platelet inhibition by clopidogrel on ex vivo platelet function tests. Whether smoking status affects the relationship between clopidogrel and clinical outcomes is unknown. **METHODS AND RESULTS:** We evaluated the relationship between smoking status (current smoker, former smoker, or never-smoker) and treatment with clopidogrel on the risk of all-cause, cardiovascular, and cancer mortality among the 12 152 participants from the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic

Stabilization, Management, and Avoidance) trial who had established cardiovascular disease. Current smoking was associated with an increase in all-cause (adjusted hazard ratio [HR] 2.58, 95% confidence interval [CI] 1.85 to 3.60), cardiovascular (HR 2.26, 95% CI 1.48 to 3.45), and cancer (HR 3.56, 95% CI 1.96 to 6.46) mortality compared with never smoking. The impact of clopidogrel on mortality differed by smoking status (P for interaction=0.018 for current smokers). Among current smokers, clopidogrel was associated with a reduction in all-cause mortality (HR 0.68, 95% CI 0.49 to 0.94); clopidogrel did not reduce all-cause mortality among former smokers (HR 0.95, 95% CI 0.75 to 1.19) or never-smokers (HR 1.14, 95% CI 0.83 to 1.58). A similar pattern was noted for cardiovascular mortality. As expected, no relationship was observed between clopidogrel and cancer mortality by smoking status. The risk of bleeding appeared to differ according to smoking status; randomized clopidogrel was associated with a significantly increased risk of severe or moderate bleeding (HR 1.62, P=0.04) among current smokers but a smaller and nonsignificant increase among never-smokers (HR 1.31, P=0.15). CONCLUSIONS: Clopidogrel therapy may be more effective in current smokers, but it may also confer a greater bleeding risk than in nonsmokers. Further studies are needed to investigate this possibility.

Cacoub, P. P., D. L. Bhatt, et al. (2009). "Patients with peripheral arterial disease in the CHARISMA trial." European Heart Journal **30**(2): 192-201.

AIMS: The aim of this study was to determine whether clopidogrel plus aspirin provides greater protection against major cardiovascular events than aspirin alone in patients with peripheral arterial disease (PAD). METHODS AND RESULTS: This is a post hoc analysis of the 3096 patients with symptomatic (2838) or asymptomatic (258) PAD from the CHARISMA trial. The rate of cardiovascular death, myocardial infarction (MI), or stroke (primary endpoint) was higher in patients with PAD than in those without PAD: 8.2% vs. 6.8% [hazard ratio (HR), 1.25; 95% CI 1.08, 1.44; P = 0.002]. Among the patients with PAD, the primary endpoint occurred in 7.6% in the clopidogrel plus aspirin group and 8.9% in the placebo plus aspirin group (HR, 0.85; 95% CI, 0.66-1.08; P = 0.18). In these patients, the rate of MI was lower in the dual antiplatelet arm than the aspirin alone arm: 2.3% vs. 3.7% (HR, 0.63; 95% CI, 0.42-0.96; P = 0.029), as was the rate of hospitalization for ischaemic events: 16.5% vs. 20.1% (HR, 0.81; 95% CI, 0.68-0.95; P = 0.011). The rates of severe, fatal, or moderate bleeding did not differ between the groups, whereas minor bleeding was increased with clopidogrel: 34.4% vs. 20.8% (odds ratio, 1.99; 95% CI, 1.69-2.34; P < 0.001). CONCLUSION: Dual therapy provided some benefit over aspirin alone in PAD patients for the rate of MI and the rate of hospitalization for ischaemic events, at the cost of an increase in minor bleeding.

Collet, J.-P., G. Montalescot, et al. (2009). "Clinical outcomes according to permanent discontinuation of clopidogrel or placebo in the CHARISMA trial." Archives of cardiovascular diseases **102**(6-7): 485-96.

BACKGROUND: Late discontinuation of clopidogrel after an acute coronary syndrome or

stent placement may be associated with a clinical rebound effect. AIMS: To describe the characteristics and evolution of patients non-compliant to study drug in the prospective, randomized, double-blind CHARISMA trial. METHODS: Of 15,603 patients aged 45 or older years with established atherothrombotic disease (coronary artery disease, stroke, peripheral arterial disease) or multiple cardiovascular risk factors, 2999 permanently interrupted (withdrawers) study drug (clopidogrel or placebo) during follow-up. The primary endpoint was first occurrence since randomization of myocardial infarction, stroke or cardiovascular death. RESULTS: Withdrawers displayed a higher risk profile and rates of death/myocardial infarction/stroke (13.5% versus 5.6%; hazard ratio [HR]: 3.18; 95% confidence interval [CI]: 3.05-3.32; $p < 0.001$) and severe bleeding (4.9% versus 0.7%; odds ratio [OR]: 7.42; 95% CI: 5.67-9.70; $p < 0.001$) versus non-withdrawers. Death/myocardial infarction/stroke occurred after an average of 228 days (95% CI: 197-258) and was less frequent in patients assigned to clopidogrel versus placebo (9.7% versus 11.9%; HR: 0.80; 95% CI: 0.64-1.00; $p = 0.051$); the rate of severe bleeding was the same (4.0% versus 4.3%; OR: 0.92; 95% CI: 0.65-1.32; $p = 0.66$). Among withdrawers, initial clopidogrel treatment was an independent correlate of survival (HR: 0.74, 95% CI: 0.59-0.93; $p = 0.011$), but not severe bleeding (OR: 0.94; 95% CI: 0.65-1.35; $p = 0.74$). Kaplan-Meier curves for the primary endpoint suggested no rebound effect or disease reactivation after discontinuation of clopidogrel compared with placebo. CONCLUSIONS: Patients who stopped medication had increased rates of ischaemic and bleeding events and mortality. Patients initially on clopidogrel had fewer ischaemic events than those on placebo; discontinuation was not associated with any clinically detectable rebound effect.

Dasgupta, A., S. R. Steinhubl, et al. (2009). "Clinical outcomes of patients with diabetic nephropathy randomized to clopidogrel plus aspirin versus aspirin alone (a post hoc analysis of the clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance [CHARISMA] trial)." *American Journal of Cardiology* **103**(10): 1359-63.

No prospective randomized trial has specifically examined the long-term outcomes of clopidogrel use in patients with chronic kidney disease. This study aimed to determine the risks and benefits of long-term clopidogrel administration in patients with diabetic nephropathy, the most common form of chronic kidney disease. We performed a post hoc analysis of the CHARISMA trial, which randomly assigned patients without active acute coronary syndrome, but with established atherosclerotic disease (symptomatic) or multiple risk factors for atherosclerotic disease (asymptomatic), to clopidogrel plus aspirin versus placebo plus aspirin. All CHARISMA patients ($n = 15,603$) were separated into the 3 groups: nondiabetic patients, diabetic patients without nephropathy, and diabetic patients with nephropathy. Within each group, outcomes of patients randomly assigned to clopidogrel were compared with those of patients randomly assigned to placebo. Outcomes in the prespecified CHARISMA subgroups of asymptomatic and symptomatic patients were also compared with respect to study drug assignment and nephropathy status. Patients with nephropathy who received clopidogrel had no difference in bleeding, but experienced significantly increased cardiovascular (CV) and

overall mortality compared with those randomly assigned to placebo. There were no differences in bleeding, overall mortality, or CV mortality for nondiabetic or diabetic patients without nephropathy who received clopidogrel versus placebo. In the asymptomatic cohort, patients with nephropathy randomly assigned to clopidogrel had significantly increased overall and CV mortality compared with placebo, whereas asymptomatic patients without nephropathy randomly assigned to clopidogrel had no significant mortality difference compared with placebo. In conclusion, this post hoc analysis suggested that clopidogrel may be harmful in patients with diabetic nephropathy. Additional studies are needed to investigate this possible interaction.

Morrow, D. A., S. D. Wiviott, et al. (2009). "Effect of the novel thienopyridine prasugrel compared with clopidogrel on spontaneous and procedural myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38: an application of the classification system from the universal definition of myocardial infarction." *Circulation* **119**(21): 2758-64.

BACKGROUND: Prasugrel is a novel thienopyridine that reduces new or recurrent myocardial infarctions (MIs) compared with clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention. This effect must be balanced against an increased bleeding risk. We aimed to characterize the effect of prasugrel with respect to the type, size, and timing of MI using the universal classification of MI. **METHODS AND RESULTS:** We studied 13 608 patients with acute coronary syndrome undergoing percutaneous coronary intervention randomized to prasugrel or clopidogrel and treated for 6 to 15 months in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI 38). Each MI underwent supplemental classification as spontaneous, secondary, or sudden cardiac death (types 1, 2, and 3) or procedure related (Types 4 and 5) and examined events occurring early and after 30 days. Prasugrel significantly reduced the overall risk of MI (7.4% versus 9.7%; hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.67 to 0.85; $P < 0.0001$). This benefit was present for procedure-related MIs (4.9% versus 6.4%; HR, 0.76; 95% CI, 0.66 to 0.88; $P = 0.0002$) and nonprocedural (type 1, 2, or 3) MIs (2.8% versus 3.7%; HR, 0.72; 95% CI, 0.59 to 0.88; $P = 0.0013$) and consistently across MI size, including MIs with a biomarker peak ≥ 5 times the reference limit (HR, 0.74; 95% CI, 0.64 to 0.86; $P = 0.0001$). In landmark analyses starting at 30 days, patients treated with prasugrel had a lower risk of any MI (2.9% versus 3.7%; HR, 0.77; $P = 0.014$), including nonprocedural MI (2.3% versus 3.1%; HR, 0.74; 95% CI, 0.60 to 0.92; $P = 0.0069$). **CONCLUSIONS:** Treatment with prasugrel compared with clopidogrel for up to 15 months in patients with acute coronary syndrome undergoing percutaneous coronary intervention significantly reduces the risk of MIs that are procedure related and spontaneous and those that are small and large, including new MIs occurring during maintenance therapy.

O'Donoghue, M., E. M. Antman, et al. (2009). "The efficacy and safety of prasugrel with and

without a glycoprotein IIb/IIIa inhibitor in patients with acute coronary syndromes undergoing percutaneous intervention: a TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) analysis." Journal of the American College of Cardiology **54**(8): 678-85.

OBJECTIVES: We evaluated the efficacy and safety of prasugrel and clopidogrel in the setting of a glycoprotein (GP) IIb/IIIa inhibitor. **BACKGROUND:** Prasugrel reduced cardiovascular events as compared with clopidogrel in TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38) but with increased bleeding. **METHODS:** Researchers in the TRITON-TIMI 38 randomized 13,608 subjects with acute coronary syndrome undergoing percutaneous coronary intervention to prasugrel versus clopidogrel. The use of a GP IIb/IIIa inhibitor was at the physician's discretion. For the current analysis, end points were examined at 30 days and were stratified by use of a GP IIb/IIIa inhibitor. **RESULTS:** A total of 7,414 subjects (54.5%) received a GP IIb/IIIa inhibitor during their index hospitalization. There was a consistent benefit of prasugrel over clopidogrel for reducing cardiovascular death, myocardial infarction, or stroke in patients who did (hazard ratio: 0.76; 95% confidence interval: 0.64 to 0.90) or did not receive a GP IIb/IIIa inhibitor (hazard ratio: 0.78; 95% confidence interval: 0.63 to 0.97, $p(\text{interaction}) = 0.83$). Prasugrel significantly reduced myocardial infarction, urgent revascularization, and stent thrombosis irrespective of GP IIb/IIIa inhibitor use. Although subjects treated with a GP IIb/IIIa inhibitor had greater rates of bleeding, the risk of Thrombolysis in Myocardial Infarction major or minor bleeding with prasugrel versus clopidogrel was not significantly different in patients who were or were not treated with GP IIb/IIIa inhibitor ($p(\text{interaction}) = 0.19$). **CONCLUSIONS:** Prasugrel significantly reduces the risk of cardiovascular events in patients with acute coronary syndromes after percutaneous coronary intervention regardless of whether or not a GP IIb/IIIa inhibitor is used. The use of a GP IIb/IIIa inhibitor does not accentuate the relative risk of bleeding with prasugrel as compared with clopidogrel.

Pride, Y. B., S. D. Wiviott, et al. (2009). "Effect of prasugrel versus clopidogrel on outcomes among patients with acute coronary syndrome undergoing percutaneous coronary intervention without stent implantation: a TRIal to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with prasugrel (TRITON)-Thrombolysis in Myocardial Infarction (TIMI) 38 substudy." American Heart Journal **158**(3): e21-6.

BACKGROUND: Prasugrel led to a significant reduction in ischemic cardiovascular events among patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) with stent implantation compared to clopidogrel. Whether this benefit extends to patients undergoing PCI without stent implantation is unknown. **METHODS:** In TRIal to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with prasugrel (TRITON)-Thrombolysis in Myocardial Infarction (TIMI) 38, patients ($n = 13\ 608$) undergoing PCI for ACS were randomized to aspirin plus clopidogrel or prasugrel. This postrandomization analysis of a prespecified subgroup was restricted to patients who underwent PCI without stent implantation ($n = 569$).

RESULTS: Patients who underwent PCI without stent implantation were older and had a

higher incidence of hypertension, diabetes, prior myocardial infarction (MI), prior coronary artery bypass (CABG) surgery, and renal dysfunction than patients who underwent stent implantation. In the group that did not undergo stent implantation, baseline characteristics were similar between patients receiving clopidogrel and prasugrel. The composite of cardiovascular death, nonfatal MI, and nonfatal stroke occurred in 14.2% of patients receiving prasugrel and 17.1% of patients receiving clopidogrel (HR 0.82, P = .27). There were significant reductions favoring prasugrel in the rates of urgent target vessel revascularization (TVR; HR 0.46, P = .040) and any TVR (HR 0.40, P = .009) and a trend toward a reduction in the incidence of nonfatal MI (HR 0.65, P = .11). CABG-related TIMI major bleeding was more frequent among patients receiving prasugrel. There were no significant interactions between treatment and PCI type. CONCLUSION: Among ACS patients who underwent PCI without stent implantation, prasugrel therapy tended to reduce clinical ischemic events and to increase bleeding events to a similar magnitude as among patients who received stents.

Wiviott, S. D., E. M. Antman, et al. (2006). "Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet Inhibition with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38)." American Heart Journal **152**(4): 627-35.

BACKGROUND: Dual antiplatelet therapy with aspirin and clopidogrel is standard for prevention of thrombotic complications of percutaneous coronary intervention (PCI). Prasugrel is a thienopyridine that is more potent, more rapid in onset, and more consistent in inhibition of platelets than clopidogrel. TRITON-TIMI 38 is designed to compare prasugrel with clopidogrel in moderate to high-risk patients with acute coronary syndrome (ACS). STUDY DESIGN: TRITON-TIMI 38 is a phase 3, randomized, double-blind, parallel-group, multinational, clinical trial. Approximately 13,000 patients with moderate to high-risk ACS undergoing PCI (9500 unstable angina/non-ST-segment elevation myocardial infarction [MI], 3500 ST-segment elevation MI) will be randomized to prasugrel 60 mg loading dose followed by 10 mg daily or clopidogrel 300 mg loading dose followed by 75 mg daily for up to 15 months. The primary end point is the time of the first event of cardiovascular death, MI, or stroke. Analyses will be performed first in the unstable angina/non-ST-segment elevation MI cohort and, conditionally, on the whole ACS population. Major safety end points include TIMI major and minor bleeding unrelated to coronary artery bypass graft surgery. CONCLUSIONS: TRITON-TIMI 38 is a phase 3 comparison of prasugrel versus clopidogrel in patients with moderate to high-risk ACS undergoing PCI. In addition, it is the first large-scale clinical events trial to assess whether a thienopyridine regimen that achieves a higher level of inhibition of platelet aggregation than the standard therapy results in an improvement in clinical outcomes.

Appendix B. Abstracts of trials identified in prior preliminary update scans #1 and #2

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.

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, $p = \text{NS}$). 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, $p = \text{NS}$). 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.

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.

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.

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.

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.

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.

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.

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 m^2), 847 were overweight (25-29.9 kg per m^2), 810 were obese (30-39.9 kg per m^2) and 113 were very obese (greater than or equal to 40 kg per m^2). 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 m^2 ($p = 0.009$). **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.

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).

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

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 ≥ 15 h pre-treatment, with a 58.8% ($p = 0.028$) reduction in the primary end point in patients pre-treated with clopidogrel ≥ 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.

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.