Low Responders to Clopidogrel at Increased Risk for ST at 30 Days

Platelet Reactivity After Clopidogrel Treatment Assessed With Point-of-Care Analysis and Early Drug-Eluting Stent Thrombosis.
Sibbing D, Braun S, et al:

J Am Coll Cardiol 2009; 53 (March 10): 849-856

Low responders to clopidogrel are at increased risk for stent thrombosis at 30 days.

**Background:** Drug-eluting stents (DES) have impacted restenosis rates significantly following percutaneous coronary intervention (PCI). Dual antiplatelet therapy has been recommended for patients undergoing PCI with DES. Even with dual antiplatelet therapy, stent thrombosis (ST) remains a potential problem. Platelet reactivity to clopidogrel is variable and may be related to ST.

**Objectives:** To assess whether platelet reactivity to clopidogrel using point-of-care testing correlates with the risk of early ST.

**Participants/Methods:** Over a 1-year period, 1608 patients underwent DES implantation for coronary artery disease (CAD). All patients were pre-treated for at least 2 hours (median, 3 to 4 hours) with 600 mg of clopidogrel. Immediately before the PCI procedure, adenosine diphosphate (ADP)-induced platelet aggregation was assessed using multiple electrode platelet aggregometry (MEA). The primary end point was definite ST at 30 days.

**Results:** The patients' MEA measurements were divided into quintiles. The upper quintile was considered the clopidogrel low responders and the other quintiles were considered normal responders. Low responders had a significantly higher risk of ST at 30 days compared to normal responders (2.2% vs 0.2%; \(P <0.0001\)). Mortality rates also tended to be lower in low responders compared to normal responders (1.2% vs 0.4%; \(P =0.07\)). The composite end point of death or ST was significantly higher in low responders (3.1% vs 0.6%; \(P <0.001\)).

**Conclusions:** Low responders to clopidogrel are at increased risk for ST at 30 days.

**Reviewer's Comments:** There are potential limitations of this study, including the small number of events and the use of a 30-day end point. However, this is an important addition to our understanding of the causes of ST. This study raises the question of regular use of an assay of platelet response in patients undergoing PCI. Further studies will reveal whether triple drug therapy or the use of one of the newer antiplatelet agents will impact ST in this patient population without increasing the risk of bleeding. (Reviewer-D. Lynn Morris, MD).

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Keywords: DES, Antiplatelet Tx, Clopidogrel, ST

Print Tag: Refer to original journal article
Adjunct Cilostazol Reduces Rate of High Post-Tx Platelet Reactivity

Randomized Comparison of Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Patients With High Post-Treatment Platelet Reactivity: Results of the ACCEL-RESISTANCE (Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Patients With Clopidogrel Resistance) Randomized Study.


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Cilostazol reduces high post-treatment platelet reactivity and increases platelet inhibition versus high maintenance dose clopidogrel.

**Background:** A combination of aspirin and a thienopyridine improves long-term outcomes and decreases stent thrombosis (ST) in patients undergoing percutaneous coronary intervention (PCI). There remains a low, but real, incidence of ST in patients undergoing PCI while receiving dual antiplatelet therapy. The use of additional agents or increasing the thienopyridine dose may lower platelet reactivity and thus the risk of ST in these patients. Cilostazol may be one of these agents.

**Objectives:** To assess the impact of cilostazol added to clopidogrel and aspirin compared to an increased maintenance dose of clopidogrel in patients with high post-treatment platelet reactivity undergoing PCI.

**Participants/Methods:** 60 patients with high post-treatment platelet reactivity after a 300-mg loading dose of clopidogrel were randomized to adjunctive cilostazol (100 mg twice daily) or high-maintenance dose clopidogrel (150 mg daily). Platelet function was assessed at baseline and at 30 days using conventional aggregometry and VerifyNow point-of-care testing.

**Results:** Baseline platelet reactivity was similar in the 2 groups. At 30 days, patients receiving triple drug therapy had a lower incidence of high post-treatment platelet reactivity than the high-maintenance dose clopidogrel group (3.3% vs 26.7%; \( P =0.012 \)). Other assays of platelet inhibition demonstrated a significantly greater platelet inhibition with triple drug therapy.

**Conclusions:** Adjunctive cilostazol reduces the rate of high post-treatment platelet reactivity and increases platelet inhibition compared to high-maintenance dose clopidogrel.

**Reviewer's Comments:** ST remains a concern after PCI even with dual antiplatelet therapy with aspirin and clopidogrel. The impact of ST can be devastating, with a high incidence of mortality in these patients. High post-treatment platelet reactivity appears to be associated with ST. This study provides insight into a potential treatment regimen for patients with high post-treatment platelet reactivity. It also raises the question of the need for routine assessment of platelet reactivity in patients undergoing PCI. (Reviewer-D. Lynn Morris, MD).

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Keywords: Cilostazol, Clopidogrel, Thienopyridine, Aspirin, PCI

Print Tag: Refer to original journal article
The concomitant use of clopidogrel and a PPI is associated with increased risk of adverse outcomes.

Background: Clopidogrel plus aspirin reduces adverse events following acute coronary syndrome (ACS). Previous studies, such as the Omeprazole Clopidogrel Aspirin (OCLA) study, found that omeprazole decreases the platelet inhibitory effect of clopidogrel following percutaneous coronary intervention (PCI). Reports have also associated this decreased inhibition of platelets with stent thrombosis (ST) following PCI. Further data have been sought to define the impact of decreased platelet inhibition in settings other than PCI.

Objectives: To assess the outcomes of patients taking clopidogrel with a proton pump inhibitor (PPI) compared to those taking clopidogrel without a PPI following hospitalization for ACS. The primary outcome was death or re-hospitalization for ACS. Secondary outcomes were re-hospitalization for ACS, revascularization procedures, and all-cause mortality.

Participants/Methods: The authors performed a retrospective cohort study of 8205 patients with ACS taking clopidogrel following discharge to assess the potential impact of a PPI on adverse events.

Results: Among the patients taking clopidogrel, 64% were prescribed a PPI at discharge, during follow-up, or both. The end point of death or re-hospitalization for ACS occurred in 20.8% of patients taking clopidogrel without a PPI compared to 29.8% of patients taking clopidogrel with a PPI. Multivariable analysis demonstrated that clopidogrel plus a PPI was associated with an increased risk of death or re-hospitalization for ACS (adjusted odds ratio [AOR], 1.25). Any period of clopidogrel plus PPI use was associated with a higher risk of death or re-hospitalization for ACS (adjusted hazard ratio, 1.27). This pattern was true for secondary outcomes including risk of re-hospitalization for ACS (14.6% vs 6.9%; AOR, 1.86) and revascularization procedures (15.9% vs 11.9%; AOR, 1.49), but not for all-cause mortality (19.9% vs 16.6%; AOR, 0.91). The findings were true for both omeprazole and rabeprazole, with other agents prescribed rarely and not able to be assessed. There was no increased risk related to the PPI agent alone. There was no difference in the risk between PPI use and no PPI use in patients not taking clopidogrel.

Conclusions: The concomitant use of clopidogrel and a PPI after hospital discharge was associated with an increased risk of adverse outcomes compared to clopidogrel without a PPI in patients with ACS.

Reviewer’s Comments: This study adds to the growing body of evidence that the concomitant use of a PPI with clopidogrel increases the adverse event rate in patients with ACS and following PCI. Previous studies suggest the mechanism for this observation is the decrease in platelet inhibition of clopidogrel due to the PPI. This has significant implications for physician prescribing habits, suggesting the need for a third drug or avoidance of PPIs in patients who have evidence of decreased platelet inhibition. It also raises the question of the usefulness of routine platelet reactivity assays in these high-risk patients. (Reviewer-D. Lynn Morris, MD).
Depression in HF patients may be associated with increased length of hospital stay, decreased use of cardiac procedures, and increased post-discharge mortality.

**Background:** Symptoms of depression are common in elderly, hospitalized, heart failure (HF) patients. Depression is also a risk factor of excessive morbidity and mortality in HF.

**Objective:** To examine in-hospital treatment and post-discharge outcomes in hospitalized HF patients with a documented history of depression from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF).

**Methods:** Patient factors associated with a depression history were assessed. Also, the association of depression with hospital treatments and mortality, early post-discharge mortality, emergency care, and re-hospitalization were evaluated.

**Results:** Among 48,612 patients from 259 hospitals, a history of depression was present in 10.6% of the patients. Depression was more common in females, whites, and those with common HF comorbidities, which included chronic pulmonary obstructive disease, anemia, insulin-dependent diabetes mellitus, and hyperlipidemia ($P < 0.001$ for all). Patients with a history of depression were also less likely to receive coronary interventions and cardiac devices ($P < 0.01$ for both) and were less likely to be referred to outpatient disease management programs, ($P < 0.001$). Hospital length of stay was also longer in patients with a depression history (7.0 vs 6.4 days; $P < 0.001$). There were 5791 patients followed-up at 60 to 90 days post-discharge. Those with a history of depression had higher mortality (8.8% vs 6.4%; $P = 0.025$). After multivariable modelling, depression history persisted as a predictor of length of hospital stay ($P < 0.001$) and post-discharge mortality ($P = 0.02$).

**Conclusions:** A history of depression at HF hospitalization may be a predictor of prolonged length of hospital stay, decreased use of cardiac procedures and post-discharge disease management, and increased 60- to 90-day mortality.

**Reviewer’s Comments:** Since both a history of depression and congestive HF are common, independent diagnoses in patient populations, the association between these 2 entities is important and is examined in this paper. These patients have fewer in-hospital cardiac procedures performed on them. The reason is unclear, apart from them having a possibly higher rate of comorbidities. However, current HF treatment guidelines do not exclude treating patients with comorbidities. These patients are also less likely to be referred to outpatient disease management programs. These findings are concerning since these patients have an increase in post-discharge mortality. Patients with depression may be a vulnerable group who may require other evidence-based treatment modalities. (Reviewer-Suraj Maraj, MD).

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**Keywords:** Depression, Heart Failure, Hospital Stay, Mortality

**Print Tag:** Refer to original journal article
**Background:** Cardiac rehabilitation (CR) reduces cardiac mortality and all-cause mortality, and improves cardiac function, blood pressure, left ventricular function, and quality of life in patients with symptomatic ischemic and valvular heart disease. Treadmill walking is a crucial component to a comprehensive CR program and increasing walking distance is a strong predictor of a reduction in cardiac risk. Patients with coronary artery disease and concomitant peripheral arterial disease (PAD) and intermittent claudication (IC) may not be able to walk with sufficient intensity to reach their target heart rate, and as a result maintain their high risk for a fatal cardiac event.

**Objective:** To determine if PAD impedes cardiac risk reduction and successful completion of CR and to see whether invasive treatment of IC in patients who cannot walk adequately to complete CR will reduce total fatal cardiac events.

**Design:** Case-controlled observational study.

**Participants:** 230 consecutive CR participants (mean age, 65 ± 11 years; 74% male) who were all capable of participation in a treadmill-based exercise program.

**Methods:** Failure of CR was defined as the inability to achieve target heart rate on treadmill. Records were reviewed for attendance, target heart rate, and Walking Impairment Questionnaire (WIQ) values, comparing the presence of PAD among failures and successes. Outcomes were compared for untreated PAD, treated PAD that interfered with CR, and treated PAD prior to CR in all subjects with PAD, using a Markov decision analysis based on published data for invasive management of IC.

**Results:** 126 of the 230 patients had complete records for review. 40% of patients failed CR. PAD was more common in the failure group compared to the success group as determined by ankle-brachial indices (ABI) and WIQ (39% vs 14%; \( P = 0.08 \) and 34% vs 17%; \( P = 0.03 \), respectively). CR failure was more common in those with claudication (76% vs 26%; \( P < 0.001 \)). Invasively treating a patient with PAD after failing CR allows them to successfully complete the program and would save an additional 54 lives per 10,000 patients compared with no intervention.

**Conclusions:** A significant cause of CR failure is PAD. Invasive treatment of these patients allows for completion of CR and subsequent reduction in fatal cardiac events.

**Reviewer’s Comments:** If a patient is able to ambulate at a target heart rate of 70% of the maximum heart rate on the pretreatment stress test, that individual will improve myocardial conditioning and endurance without risking excessive cardiac strain during exercise. This in turn reduces the risk of fatal cardiac events. Patients with IC have reduced walking speed and distance. This study is the first to show that for such patients who fail CR, invasive treatment of IC to allow for successful completion of CR will reduce their risk of cardiac mortality. (Reviewer-Debra Braverman, MD).

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Keywords: Intermittent Claudication, PAD, Cardiac Rehab

Print Tag: Refer to original journal article
Consider preoperative dialysis in patients with a creatinine level >2.5 undergoing cardiac surgery.

**Background:** It is well known that renal failure after cardiac surgery is an independent risk factor for increased mortality. Therefore, all efforts should be made to avoid this dreaded complication. Preoperative renal insufficiency contributes significantly to the risk of postoperative renal failure and is a marker for elevated morbidity and mortality associated with cardiac surgery. Several intraoperative strategies that have been employed to help lessen this risk include keeping the mean blood pressure at an adequate level, performing ultrafiltration while on bypass, and the selective use of off pump bypass.

**Objective:** To determine if preoperative dialysis in a select group of patients with elevated serum creatinine would decrease the postoperative morbidity and mortality associated with cardiac surgery.

**Design:** Retrospective, single-center review of patients undergoing cardiac surgery who had an elevated risk of postoperative renal failure.

**Participants/Methods:** 116 patients with a creatinine clearance ≤30 mL undergoing cardiac surgery between 1996 and 2006 were chosen. Group A consisted of patients who did not receive dialysis preoperatively (n=84), and group B consisted of patients who received 1 or 2 sessions of dialysis the day prior to surgery (n=32). Ultrafiltration was carried out in some patients intraoperatively. Postoperative dialysis was performed as needed.

**Results:** 28 patients were propensity matched and compared. There were significantly fewer neurologic complications, gastrointestinal complications, major adverse events, and a shorter postoperative length of stay in the group that received preoperative dialysis (group B). Not significant, but favorable trends were also seen in this group when analyzing postoperative fluid retention and decreased rate of multiorgan failure. More patients in the dialysis group were discharged to home.

**Conclusions:** Patients with non-dialysis-dependent renal failure who are dialyzed preoperatively show significant improvements in postoperative outcomes after cardiac surgery.

**Reviewer's Comments:** Although this paper has some major limitations, I found it to be important for acknowledging the possibility of preoperative dialysis in non-dialysis-dependent patients before cardiac surgery. The retrospective nature of the study, the small number of patients who were propensity matched, and the variable selection and treatment methods are some of its limitations. However, I applaud the authors for attempting a new treatment strategy that may help in the management of these difficult patients. I have no doubt that it was difficult to convince the nephrologists to dialyze these patients preoperatively. Amazingly, only 50% of these patients were discharged on home dialysis and these patients were showing a trend towards renal recovery with a decreasing creatinine. This study needs to be done as a prospective, randomized trial to obtain cleaner data and to gain support for this technique, which I believe will be helpful in decreasing renal failure and improving outcomes after cardiac surgery. (Reviewer-Linda J. Bogar, MD).

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Keywords: Renal Insufficiency, Dialysis, CABG

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The overall incidence of MI is stable, but the severity is decreasing.

**Background:** Mortality rates in coronary heart disease are declining across the United States. Yet, the incidence of acute myocardial infarction (MI) is unchanged, which suggests that the severity of MI may be declining. The Atherosclerosis Risk in Communities (ARIC) Study provides validated data from 4 geographically diverse communities in the U.S.

**Objective:** To monitor hospital discharges of acute MI in 35- to 74-year-olds in 4 ARIC communities from 1987 through 2002.

**Methods:** Information was obtained from medical records on presenting symptoms, chest pain, medical history, and cardiac biomarkers during the first 4 days. Hospitalized MI was defined using various combinations of electrocardiogram (ECG) patterns, cardiac chest pain, and biomarkers. Both definite and probable MI patients were included in the study.

**Results:** 10,285 subjects with MI were included; approximately 33% were women. During the study, there was no change in time from symptom onset to hospitalization; approximately 66% of the patients delayed ≥2 hours before hospital arrival. Revascularization within 24 hours for non-ST-segment elevation MI (STEMI) did not change, but there was a significant increase in revascularization of STEMI patients. Thrombolytic therapy declined, while percutaneous coronary intervention increased. Coronary artery bypass grafting (CABG) rates were stable. Age, sex, and race adjusted percent of cases with major ECG abnormalities decreased. Maximum creatine kinase (CK) and (CK)-MB values declined significantly, whereas maximum troponin values showed a small nonsignificant decrease. Re-analysis, excluding MIs detected only by biomarkers, showed slight attenuation of results but did not significantly alter findings. "Definite" MI declined, while "probable" MI rose. Several indexes of MI severity exhibited nonlinear trends. Several ECG markers showed an early increase in severity followed by a decrease. The proportion with abnormal biomarkers showed an initial decline with a subsequent increase.

**Conclusions:** This study provides evidence of decreasing severity of MI. Race and sex specific results were consistent with overall results. Biomarker and ECG indicators improved in both whites and blacks. This reduction in severity, and other factors, probably explains the declining death rates for coronary heart disease.

**Reviewer's Comments:** Several reasons may be contributing to decreasing MI severity, including preventive efforts and improved hospital care. This study suggests both factors were active. The time delay until patients seek treatment might also influence severity but was not observed to change. There has been little progress on this issue. During the study, there was a rapid increase in use of evidence-based therapies for acute MI, including interventions and proven medications. Troponins are more sensitive than CK and (CK)-MB, and their introduction likely changed the ascertainment of acute MI and its severity. However, the ARIC definition of acute MI is strongly influenced by ECG criteria. Re-analysis of the data excluding biomarker-driven MIs, showed associations were attenuated, but largely unchanged. (Reviewer-Gregg S. Pressman, MD).

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Keywords: MI Severity, ARIC Study

Print Tag: Refer to original journal article
TIC caused by focal atrial tachycardia is reversible with treatment of underlying cause.

**Background:** Tachycardia-induced cardiomyopathy (TIC) is an increasingly-recognized cause of left ventricular (LV) dysfunction and consequent heart failure. Reliable data on the cause, incidence, and treatment outcome of this entity are lacking.

**Objective:** To describe the incidence, tachycardia characteristics, patient characteristics, and outcome after catheter ablation in patients with TIC complicating focal atrial tachycardia (FAT).

**Participants/Methods:** The study population included 345 patients undergoing catheter ablation for FAT over a 10-year period in Australia. All patients had failed anti-arrhythmic drug therapy. Patients with a LV ejection fraction (LVEF) of <50% were defined as having TIC if other causes of LV dysfunction were excluded. Comparisons were made between FAT patients with TIC and those without. Most patients underwent successful radiofrequency ablation (RFA) of the tachycardia focus.

**Results:** The overall study population was 40% male, with a mean age of 50 years (range, 9 to 85 years). TIC was diagnosed in 30 patients (10%) with a mean LVEF of 35%. Compared to controls, the TIC group was significantly younger (39 vs 51 years) and more likely to be male (60% vs 38%). The TIC patients had slower atrial tachycardia rates and slower ventricular response rates. A strong relationship was found between incessant or frequent paroxysmal tachycardia and the development of TIC. FAT foci around the atrial appendages and the pulmonary veins were associated with a higher incidence of both incessant tachycardia and TIC. Long-term success without tachycardia recurrence in the TIC group, at a mean follow-up of 23 months, was 87% without use of medications. Normalization of LV function occurred in 97% (29 of 30) of the TIC patients at mean of 2.8 ± 2 months. Long-term follow-up (20 ± 28 months) did not demonstrate any episodes of syncope or sudden cardiac death in the TIC group. **Conclusion:** TIC is not infrequent in patients with FAT. It is more likely to occur in patients with incessant and relatively slow tachycardia. Normalization of LV function occurs a few weeks following RFA, with no apparent long-term adverse outcomes.

**Reviewer's Comments:** There has been a recent increase in the diagnosis of TIC that is likely due to the increased awareness of and education about this disease entity. A thorough exclusion of all other causes of cardiomyopathy is extremely important. When the diagnosis is correct and patients get adequate therapy, pharmacologic or catheter-based, the prognosis appears to be favorable. Additional studies are needed to verify whether normalization of LV function returns the risk of sudden cardiac death back to baseline. The need for long-term pharmacological treatment (ie, beta blockers and angiotensin-convertin enzyme inhibitors) to prevent recurrence of LV dysfunction after curing the tachycardia is another important question awaiting a definitive answer. (Reviewer-Khalid Almuti, MD).

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Keywords: Tachycardia-Induced Cardiomyopathy

Print Tag: Refer to original journal article
The use of DES in STEMI is safe and reduces target vessel revascularization.

**Background:** Controversy exists regarding the use of drug-eluting stents (DES) in the setting of acute ST-segment elevation myocardial infarction (STEMI).

**Objective:** To compare outcomes between DES and bare-metal stents (BMS) in STEMI.

**Methods:** The endpoints studied included death, myocardial infarction (MI), target lesion revascularization, and stent thrombosis. A secondary analysis was also done using registry studies. Several databases, including MEDLINE, EMBASE and Cochrane Library, were searched for studies that compared BMS to DES (Cypher or Taxus) in STEMI. The initial search yielded 13 randomized control studies and 18 registry studies.

**Results:** There were a total of 7352 patients in the 13 randomized clinical trials, with 4515 randomly assigned to DES and 2837 assigned to BMS. The mean ages ranged from 59 to 63 years, and almost 50% of the culprit lesions were in the left anterior descending artery. Ten percent to 21% of the patients were diabetic, and the use of clopidogrel ranged from 6 to 12 months. There were no statistically significant differences between DES and BMS in mortality (3.7% vs 4.3%), myocardial infarction (3.4% vs 3.8%), or stent thrombosis (2.7% vs 2.6%). The target vessel revascularization was significantly lower in the DES group (5.3% vs 7.7%). Somewhat similar results were found in the registry studies. There was an apparent favorable effect on mortality at year 1 for DES in the registry studies that disappeared after adjusting for publication bias. The magnitude of reduction in target vessel revascularization with DES was also lower in the registry studies.

**Conclusions:** In a large number of patients in both randomized clinical trials and registry data, DES seem to be as safe as BMS in STEMI, with the added benefit of lower target vessel revascularization.

**Reviewer's Comments:** Numerous trials have established the safety and efficacy of DES in both stable coronary artery disease and acute coronary syndromes. However, the pivotal trials that led to the Food and Drug Administration approval of sirolimus-eluting stents and paclitaxel-eluting stents (SIRIUS and TAXUS IV) excluded patients with STEMI. Thus, the use of DES for STEMI still remains "off-label." There have been concerns about stent thrombosis in some observational studies when DES is used in STEMI. This large meta-analysis of 13 randomized clinical trials and 18 registries confirm the benefit of DES in reducing target vessel revascularization in the setting of STEMI, without increasing the risk of death, myocardial infarction or stent thromboses. These results did not change when accounting for the size of the trial, follow up duration, and duration of clopidogrel use. Only 2 trials had longer than 24-month follow-up; thus it is not known whether these results can be expected long term. (Reviewer-Anoop C. Parameswaran, MD).

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Keywords: Stent, STEMI, Meta-Analysis

Print Tag: Refer to original journal article
Compared with bare-metal stents, for those with acute ST-segment elevation myocardial infarction, drug-eluting stents reduce restenosis and recurrent ischemia, but do not change mortality or reinfarction risk.

**Background:** In patients with acute ST-segment elevation myocardial infarction (STEMI), bare-metal stents (BMS) (compared with balloon angioplasty) reduce the risk of recurrent ischemia and repeat percutaneous coronary intervention (PCI). The value and safety of drug-eluting stents (DES) in the setting of STEMI remains controversial.

**Design/Objective:** This international, prospective, randomized trial compares paclitaxel-eluting stents with otherwise identical BMS in patients with acute STEMI.

**Methods:** Patients with infarct-related artery size between 2.25 and 4.0 mm without excessive tortuosity or severe calcification were randomized. Patients with a high risk of hemorrhage or the inability to take clopidogrel for 6 months were excluded. Anatomic exclusions included stenting of an unprotected left main coronary artery, anticipated stent length of >100 mm, bifurcation lesions with the need for stenting of both vessels, and infarction due to stent thrombosis. Clopidogrel was given for at least 6 months and recommended for at least 1 year. Clinical evaluation occurred intermittently for 1 year, and angiography was performed at 13 months. Two primary 1-year outcomes were assessed, including ischemia-driven target lesion revascularization and a composite safety end point that included death, reinfarction, stroke, and stent thrombosis.

**Results:** 3006 patients were randomized in a 3:1 ratio to receive either DES or BMS. Baseline clinical and anatomic characteristics were generally well matched. Median age was 60 years, and 77% were men. Compliance with aspirin and clopidogrel was good, although clopidogrel use was slightly higher in the DES group at 6 months (95% vs 88%). The rate of the primary efficacy end point, ischemia-driven target lesion revascularization, was significantly lower in the DES group (4.5% vs 7.5%). The rate of the primary safety end point was similar between the groups (8.1% vs 8.0%). The individual components of the safety end point were also similar. Angiography at 13 months demonstrated a significantly lower rate of restenosis in the DES group versus the BMS group (10.0% vs 22.9%).

**Conclusions:** For patients with acute STEMI, the use of DES, compared with otherwise identical BMS, resulted in less restenosis and less recurrent ischemia requiring repeat revascularization. There were no differences in the composite safety end point or in any of the individual components.

**Reviewer's Comments:** This trial confirms and extends the results from prior small randomized trials of stent therapy for acute STEMI. Although the use of DES results in less restenosis, it does not change mortality or reinfarction risk at 1 year. Longer-term data are needed to more fully evaluate the risk and benefit of DES. Furthermore, the use of DES mandates the use of dual antiplatelet therapy for at least 1 year to reduce the risk of in-stent thrombosis. For patients unable to comply with clopidogrel therapy, the use of DES may be hazardous. (Reviewer-Craig M. Oliner, MD).

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**Keywords:** Acute MI, Stents, PCI

**Print Tag:** Refer to original journal article
Weight-loss supplements contain a variety of ingredients that are potentially life-threatening.

**Background:** Obesity is reaching epidemic proportions in the United States, and with this rise in obesity, over-the-counter weight-loss supplements have become increasingly popular and are often taken without oversight from a health care professional. In addition, these supplements are not typically regulated by the Food and Drug Administration, and it is unclear what adverse effects these supplements may cause.

**Objective:** To define the arrhythmogenic and life-threatening cardiac adverse effects associated with weight-loss supplements obtained and purchased on the internet.

**Methods:** 12 different weight-loss supplements were purchased through 3 popular web search engines using the term "weight-loss supplements." On the websites selling the products, all packages and inserts were read for potential cardiovascular adverse effects. Comprehensive searches were then performed in Medline and the Natural Medicines Comprehensive Database for listed ingredients to identify reported life-threatening cardiac or arrhythmogenic adverse events.

**Results:** None of the websites or package inserts contained warnings of potential adverse effects. Sixty different ingredients were listed for the 12 products. Of these ingredients, 42 were herbal extracts, 5 were synthetic compounds, 4 were minerals, and 9 were vitamins or other organic substances. Eight of the substances had at least 2 reported life-threatening cardiac events or deaths. One product contained ma huang (ephedra) despite marketing bans against ephedra products in the U.S. Reported adverse effects included cardiomyopathy, myocarditis, cardiac arrest, myocardial infarction, hypokalemia, metabolic acidosis, prolongation of QT, torsades de pointes, premature atrial contractions, ventricular fibrillation, syncope, and death.

**Conclusions:** Easily accessible weight-loss supplements contain a variety of ingredients with possible significant cardiac and arrhythmogenic adverse events.

**Reviewer's Comments:** This straightforward analysis provides an interesting and somewhat frightening review of available weight-loss supplements. Given that over 15% of Americans have apparently taken these types of supplements, this information cannot be ignored. This paper contains a good primer on specific ingredients that was beyond the scope of this review and should be referred to for preliminary background. (Reviewer-Sumeet K. Mainigi, MD).

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Keywords: Obesity, Supplements, Alternative Medicine

Print Tag: Refer to original journal article
Incarceration is associated with hypertension and left ventricular hypertrophy in young adults.

Background/Objective: Incarceration is associated with increased cardiovascular disease mortality. Recent data suggest an increased risk of immediate mortality among recently released prisoners, with the second most common cause of death being from cardiovascular disease. However, the mechanisms of this association have not been well documented in prospective studies.

Methods: The independent association of prior incarceration with incident hypertension, diabetes mellitus, and dyslipidemia using the Coronary Artery Risk Development in Young Adults (CARDIA) study, a cohort of young adults aged 18 to 30 years old at enrollment in 1985 to 1986, balanced by sex, race (black and white) and education (high school education or less), was examined. The association of incarceration with left ventricular (LV) hypertrophy on echocardiography was also assessed, as was access to appropriate health care services.

Results: Of the 4350 participants, 288 (7%) reported a history of prior incarceration. Incident hypertension in young adulthood was more common among former inmates than in those without incarceration history (12% vs 7%; OR, 1.7; 95% CI, 1.2 to 2.6). This association persisted after adjustment for smoking, alcohol and illicit drug use, and family income (adjusted OR [AOR], 1.6; 95% CI, 1.0 to 2.6). Also, incarceration was significantly associated with incident hypertension in those groups with the highest prevalence of prior incarceration (black men and less-educated participants). Echocardiographic imaging revealed that former inmates were more likely to have LV hypertrophy (AOR, 2.7; 95% CI, 0.9 to 7.9). Former inmates also reported no regular source for medical care. There were no significant difference between cholesterol levels and diabetes mellitus rates due to a history of incarceration. Conclusions: Among young adults, incarceration is associated with future hypertension and LV hypertrophy. Former inmates are also less likely to have access to health care.

Reviewer's Comments: Incarceration has become more frequent among young adults. This paper illustrates the important association between incarceration, future hypertension and left ventricular hypertrophy. The exact mechanisms are not known, but it is possible that the stress of incarceration is associated with an increase or dysregulation of catecholamine or stress hormone levels. This may increase the subsequent development of hypertension. Appropriate identification and treatment of hypertension may help in reducing cardiovascular disease risk among formerly incarcerated individuals. (Reviewer-Suraj Maraj, MD).

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Keywords: Incarceration; LV Hypertrophy; Hypertension

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Adenosine cardiac magnetic resonance imaging is useful to assess the functional significance and prognosis in patients with intermediate degrees of coronary artery stenosis.

**Background:** The ischemic significance of intermediate degrees of coronary stenosis by invasive coronary angiography can be difficult to determine. Prior studies have shown that revascularization guided by functional significance of coronary lesions either by fractional flow reserve or by nuclear stress testing is superior to revascularization guided by the anatomic degree of stenosis.

**Objective:** To assess the usefulness of adenosine cardiac magnetic resonance (CMR) imaging to assess the prognosis of patients with intermediate degrees of coronary stenosis.

**Participants/Methods:** 81 patients (75.6% male; mean age, 64.2 years) with ≥1 lesion(s) by invasive coronary angiography that was 50% through 75% diameter stenosis were studied by adenosine CMR. All patients, regardless of the degree of ischemia, received optimal medical treatment. The primary end points included all-cause death, stroke, or acute coronary syndromes. The secondary end points included target vessel revascularization (TVR), angina pectoris, or dyspnea.

**Results:** 45 patients had perfusion defects (average of 2.4 ± 1.4 segments) by CMR. There were no statistically significant differences in the mean, age, gender, or risk factors among those with and without perfusion defects. At the end of 30 ± 8 months of follow-up, there were no strokes or deaths in either group. However, 17.8% of those with perfusion defects had non-ST-segment elevation myocardial infarction and 2% had unstable angina. The number of ischemic segments in these patients was also higher. No events occurred in those without perfusion defects. At 18 ± 8 months of follow-up, there was significantly more TVR (28.9% vs 5.5%) and angina (53.3% vs 11.1%) in those with perfusion defects. At 30 ± 8 months of follow-up, those with perfusion defects still had significantly more TVR (37.8%), but there was no difference in patients with intermediate degrees of coronary stenosis, which predicts the occurrence of major cardiac adverse events.

**Reviewer's Comments:** This study demonstrates that the presence and degree of ischemia detected by CMR, in those with intermediate degrees of coronary stenosis, is associated with major cardiac adverse events. Despite optimal medical therapy, those with ischemia had higher event rates than those without ischemia. However, this study does not allow us to make conclusions on whether revascularization in those with ischemia would improve outcomes; although this would seem logical. The nuclear sub-study of the COURAGE trial showed that there was a greater reduction in ischemia in those treated with PCI, and an exploratory analysis suggested that the risk of death or myocardial infarction rises with the degree of ischemia. CMR has tremendous potential to be a "one-stop shop" for assessing the degree of anatomic stenosis, its functional significance, and prognosis without the dangers of radiation or invasive testing. (Reviewer-Anoop C. Parameswaran, MD).

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**Keywords:** Intermediate Angiographic Severity, Perfusion, Adenosine Stress CMR

**Print Tag:** Refer to original journal article
Both resistance and aerobic exercise have beneficial effects on endothelial function.

**Background/Objective:** Endothelial dysfunction is associated with a less favorable prognosis in patients with coronary artery disease. Exercise training can improve endothelial function, but there is still controversy over the level and format of exercise that yields optimal beneficial effects. Most studies concentrate on aerobic exercise. No study compares the impact of resistance versus aerobic exercise on endothelial function.

**Methods:** All patients were referred from a cardiac rehabilitation program after a first myocardial infarction (MI). Endothelial function was assessed using 2-D ultrasonography at baseline and after cuff inflation for 5 minutes looking for hyperemia (flow-mediated dilatation). Patients were then given 0.3 mg of sublingual nitroglycerin (NTG) to assess endothelial-independent vasodilitation. Patients were randomized to 4 groups: (1) aerobic training consisting of moderate exercise 4 days a week for 4 weeks at 75% of peak exercise heart rate; (2) resistance exercises at 60% of pre-training maximum voluntary contraction, 4 days/week for 4 weeks; (3) aerobic and resistance training combined; and (4) no training. All exercise groups reached the same average heart rate during the training period. During detraining, no patient underwent structured sessions of physical activity.

**Results:** After cuff release, the brachial artery diameter increased similarly in all groups at rest. Significant improvement was seen in brachial artery endothelial dependent relaxation (flow mediated dilatation [FMD]) after training in all the exercise groups. The control group also showed improvement (but to a lesser extent) probably related to post-MI improvement. NTG induced similar significant vasodilitation in all groups. Peak VO\textsubscript{2} increased in all trained groups but not in the untrained group. FMD was lower in all trained groups after detraining, but there was no change in the endothelial independent vasodilitation. Functional capacity decreased in the trained groups after detraining, but was unchanged in the control group. Von Willebrand factor decreased 16% in all trained groups.

**Conclusions:** An important degree of endothelial dysfunction was found in a large homogeneous group of patients 3 weeks after an MI when compared to healthy patients. Exercise helped restore endothelial function in all the trained patients. There was no difference among aerobic, resistance, or combined training.

**Reviewer's Comments:** Resistance as well as aerobic exercise has beneficial effects on the vascular endothelium in patients post MI. Including various forms of exercise in a cardiac rehabilitation program will make it more interesting and foster better adherence. (Reviewer-Marjorie Stanek, MD).

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Keywords: Exercise Training, Detraining, Post-MI

Print Tag: Refer to original journal article
Adding clopidogrel to aspirin in nonvalvular atrial fibrillation reduces stroke but increases major bleeding.

**Background:** Vitamin K antagonists (VKA) reduce the risk of stroke in nonvalvular atrial fibrillation (AF) but at the risk of increased risk of bleeding. Aspirin also reduces stroke risk but much less effectively. For AF patients unsuitable for VKA therapy, it is unclear if adding clopidogrel to aspirin is beneficial.

**Objective:** To evaluate the role of clopidogrel plus aspirin in preventing stroke in patients with atrial fibrillation.

**Methods:** Patients with AF and increased risk of stroke (≥75 years of age; hypertension; previous stroke, transient ischemic attack, or non-central nervous system (CNS) embolus; ejection fraction <45%; peripheral vascular disease; or age 55 to 74 years plus diabetes or coronary disease) were randomized to aspirin (75 to 100 mg) plus placebo or aspirin plus clopidogrel. The primary outcome was a composite of stroke, non-CNS embolism, myocardial infarction (MI), or vascular death. Major bleeding was defined as fatal hemorrhage, a drop in hemoglobin level of ≥5.0 g/dL, hypotension requiring pressors, intraocular bleeding, bleeding requiring surgery, intracranial hemorrhage, or transfusion of ≥4 units of blood.

**Results:** 7554 patients were randomized with a median follow-up of 3.6 years; 43 patients were lost to follow-up. The primary end point occurred in 6.8%/year with aspirin/clopidogrel versus 7.6%/year with aspirin/placebo (RR, 0.89; 95% CI, 0.81 to 0.98; \( P = 0.01 \)). This difference was mostly driven by decreased stroke risk, 2.4% with aspirin/clopidogrel versus 3.3% with aspirin/placebo (RR, 0.72; 95% CI, 0.62 to 0.83; \( P < 0.001 \)). Major bleeding occurred in 251 patients receiving clopidogrel (2.0%/year) versus 162 receiving placebo (1.3%/year) (\( P < 0.001 \)). When the primary outcome and major bleeding were combined, there was no significant difference between groups (\( P = 0.54 \)).

**Conclusions:** In AF patients judged unsuitable for VKA therapy, the addition of clopidogrel to aspirin reduced major vascular events but at the risk of increased major bleeding.

**Reviewer’s Comments:** This is the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) A study. The same group of investigators previously published the ACTIVE W study comparing aspirin plus clopidogrel with VKA in nonvalvular AF. ACTIVE W was halted early because of the clear superiority of anticoagulant therapy in prevention of vascular events (mostly stroke). The current study (ACTIVE A) looks at aspirin plus clopidogrel versus aspirin alone for prevention of vascular events in patients with nonvalvular AF. It shows little tangible benefit when adding clopidogrel to aspirin. Though there was a significant decrease in stroke rate, this came at the expense of a small but statistically significant increase in major bleeding. Many of the patients in this study, as in clinical practice, had no absolute contraindications to VKA therapy and perhaps should have been treated with formal anticoagulation (absolute stroke risk with VKA therapy in ACTIVE W was 1.4%/year versus 2.4%/year with aspirin plus clopidogrel in ACTIVE A). In addition, it should be kept in mind that dual antiplatelet therapy has a significant attendant risk of major bleeding, particularly in elderly, female, and chronic kidney disease patients. (Reviewer-Gregg S. Pressman, MD).
Warfarin, Aspirin, Clopidogrel Do Not Affect Mortality in Heart Failure Patients

Randomized Trial of Warfarin, Aspirin, and Clopidogrel in Patients With Chronic Heart Failure: The Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) Trial.
Massie BM, Collins JF, et al:
Circulation 2009; 119 (March 31): 1616-1624

There is no difference between warfarin, aspirin, or clopidogrel treatment groups in mortality, MI, stroke among heart failure patients.

Background/Objective: Heart failure is associated with a hypercoagulable state. Previous studies have shown benefit to anticoagulation but mostly in patients with associated atrial fibrillation or valvular disease. No large prospective trial of heart failure patients with reduced ejection fraction in sinus rhythm has evaluated the use of warfarin versus antiplatelet agents.

Participants: 1587 patients were enrolled in 142 centers. All had symptomatic heart failure (NYHA class II to IV), ejection fraction ≤35% and were in sinus rhythm.

Design/Methods: This was a prospective, randomized trial with 3 treatment arms: aspirin 162 mg; clopidogrel 75 mg daily (double blind); or open-label warfarin (target international normalized ratio [INR], 2.5 to 3.0). The primary end point was the composite of all-cause mortality, nonfatal MI, and nonfatal stroke. Secondary end points included the 3 components of the primary end point and hospitalizations for heart failure.

Results: For the primary end point, the hazard ratios were: warfarin versus aspirin, 0.98 (95% CI, 0.86 to 1.12; P = 0.77); clopidogrel versus aspirin, 1.08 (95% CI, 0.83 to 1.40; P = 0.57); and warfarin versus clopidogrel, 0.89 (95% CI, 0.68 to 1.16; P = 0.39). Analysis based on all strokes (fatal and nonfatal) favored warfarin. However, when central nervous system (CNS) bleeding was added in, no significant differences were found between groups. There were more hospitalizations for heart failure in the aspirin versus warfarin group though time to heart failure admission was similar.

Conclusions: The 95% confidence limits effectively excluded a 20% difference between warfarin and aspirin for both the primary end point and total mortality. Similarly, 90% CIs exclude a 20% difference favoring clopidogrel over aspirin. There was a low incidence of stroke (only 1.0 event per 100 patient-years of follow-up in the non-warfarin group). Compared with aspirin patients, the warfarin group had fewer hospitalizations for heart failure. Although warfarin was associated with a lower stroke risk, when CNS bleeding and stroke were combined, this difference disappeared.

Reviewer’s Comments: Because of slow enrollment and early termination, this study was underpowered. Nevertheless, it excludes any major benefit of warfarin or clopidogrel for prevention of the primary end point. There was increased heart failure hospitalization in the aspirin group, which may have been due to a negative interaction with angiotensin converting enzyme (ACE) inhibitor therapy; previous analyses of ACE inhibitor studies have raised concerns that aspirin diminishes the benefit of such therapy. (Reviewer-Gregg S. Pressman, MD).

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Keywords: Warfarin, Aspirin, Clopidogrel, Heart Failure

Print Tag: Refer to original journal article
Ischemia After ACS Detected by Continuous EKG Monitoring

Ischemia Detected on Continuous Electrocardiography After Acute Coronary Syndrome: Observations From the MERLIN-TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction 36) Trial.

Scirica BM, Morrow DA, et al:

J Am Coll Cardiol 2009; 53 (April 21): 1411-1421

Ischemia detected by continuous EKG monitoring after ACS is frequent and associated with a poor prognosis.

**Background:** There are no recent studies looking at the occurrence of ischemia on ambulatory electrocardiographic (EKG) recordings after acute coronary syndromes (ACS) treated using modern invasive strategies and potent antiplatelet agents.

**Objective:** To evaluate the association between ischemia detected by ambulatory EKG recordings and cardiovascular outcomes after ACS.

**Methods:** The MERLIN-TIMI 36 trial was a large randomized control trial of 6560 patients hospitalized with non-ST-segment elevation MI (non-STEMI) who were randomly assigned to ranolazine or placebo in addition to standard treatment. Approximately 97% of these patients had continuous EKG monitoring for 7 days and were analyzed for this study. Outcomes after a median of 348 days were analyzed.

**Results:** 1271 (20%) patients developed evidence of ischemia on continuous EKG monitoring. In two-thirds of the patients, ischemia occurred in the first 48 hours of monitoring. There was a lower incidence of ischemia after 72 hours in the invasively treated patients (2.8% vs 5%). Those with ischemia had a significantly higher incidence of cardiovascular death (7.7% vs 2.7%), MI (9.4% vs 5%), and recurrent ischemia (17.5% vs 12.3%). Ischemia detected on EKG was an independent predictor of cardiovascular death even after adjusting for confounders (HR, 2.46; \( P <0.001 \)). Ranolazine did not decrease the frequency of ischemia detected by continuous EKG monitoring. **Conclusion:** Ischemia detected by continuous EKG monitoring is associated with a higher risk of cardiovascular death, MI, and recurrent ischemia after acute ACS.

**Reviewer's Comments:** It is well known that evidence of ischemia detected either by EKG or by nuclear perfusion studies is a marker of recurrent ischemia and MI. Very few studies have shown an association between ischemia detected by continuous EKG and cardiovascular mortality. This study demonstrates that ischemia occurs frequently after conventional optimal medical or invasive treatment for non-STEMI. This ischemia is not only associated with recurrent ischemia and MI but also with cardiovascular death. Even in low clinical risk patients (normal admission EKG, negative troponin, BNP <80 pg/mL), evidence of ischemia on ambulatory EKG conferred a higher risk of cardiovascular death (5.1 % vs 0.6%). Interestingly, although ranolazine reduced recurrent symptomatic ischemia in the MERLIN-TIMI 36 trial and reduces angina frequency and prolongs the time to onset of ST-segment depression in stable angina, it failed to reduce ischemic EKG changes early after non-STEMI. This is likely due to the different etiologies of ischemia in early ACS compared with chronic ischemia. Patients are routinely monitored on telemetry floors after ACS and ischemic changes detected on continuous EKG recordings may help to identify high-risk patients. (Reviewer-Anoop C. Parameswaran, MD).

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Keywords: Acute Coronary Syndrome, Ranolazine, Holter

Print Tag: Refer to original journal article
Outcomes of Clopidogrel Use Prior to CABG

**Outcomes Following Pre-Operative Clopidogrel Administration in Patients With Acute Coronary Syndromes Undergoing Coronary Artery Bypass Surgery: The ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) Trial.**

Ebrahimi R, Dyke C, et al:


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**Clopidogrel use prior to CABG in patients with NSTEMI is associated with improved outcomes.**

**Background:** The up-stream use of clopidogrel improves outcomes in patients with acute coronary syndromes (ACS). However, given the concern with bleeding risk in the minority of patients who may subsequently require coronary artery bypass grafting (CABG), physicians are reluctant to initiate clopidogrel therapy. Also, the benefits of early initiation of clopidogrel in those ultimately undergoing CABG are not clear.

**Objective:** To assess the bleeding risk and ischemic benefits of clopidogrel use prior to CABG.

**Design/Methods:** This was a retrospective analysis of 11.1% (1539) of patients with non-ST-segment elevation myocardial infarction (NSTEMI) who underwent CABG in the ACUITY trial. A 5-day washout period was recommended in those who received clopidogrel prior to CABG if possible. Comparison was made between those exposed to clopidogrel and those not exposed to clopidogrel before CABG.

**Results:** 50.9% of patients received clopidogrel before CABG. There was a significantly lower 30-day incidence of composite ischemia (death, MI, unplanned revascularization) in those exposed to clopidogrel (12.7% vs 17.3%). This was primarily driven by lower myocardial infarctions in the clopidogrel-exposed group (8.8% vs 4.5%). The rate of non-CABG-related major bleeding was similar between the 2 groups (3.4% vs 3.2%). The rate of CABG-related bleeding, transfusion, re-operation for bleeding, and chest tube output were also similar between the 2 groups. The duration of hospital stay, however, was higher in those exposed to clopidogrel (12 vs 8.9 days).

**Conclusions:** Clopidogrel exposure prior to CABG reduces 30-day composite ischemia without increasing major bleeding complications but increases the length of hospital stay.

**Reviewer’s Comments:** This trial confirms the benefits of clopidogrel in reducing ischemia in the subset of patients exposed to clopidogrel undergoing CABG, without increasing the risk of major bleeding. This lends support to guideline recommendations for up-stream clopidogrel use in NSTEMI. In secondary analysis, the rates of major non-CABG-related bleeding and post-CABG bleeding were not increased in those requiring CABG within 5 days of clopidogrel exposure. One must still be cautious, however, as there was an increased need for blood transfusions in this group. The bleeding risk will likely be higher if a 600-mg loading dose rather than the 300-mg loading dose (like in this study) is used. These results are consistent with data from the CURE trial were. Although there was no overall increase in the risk of bleeding, those patients undergoing CABG within 5 days of clopidogrel exposure had higher bleeding (6.3 vs 9.6%). Thus a wash out period of 5 days, if possible, still seems prudent. Even if CABG is performed earlier than the recommended 5-day washout period, it is reassuring that the major bleeding rates were not significantly increased. (Reviewer-Anoop C. Parameswaran, MD).

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**Keywords:** Clopidogrel, CABG, Bleeding

**Print Tag:** Refer to original journal article
Large Aortic Plaques Increase Risk of Recurrent Stroke, Death

Aortic Arch Plaques and Risk of Recurrent Stroke and Death.

Di Tullio MR, Russo C, et al:

Circulation 2009; 119 (May 5): 2376-2382

Recurrent stroke risk is high when large, complex aortic atheroma is found on TEE.

**Background/Objective:** Aortic arch plaques are a risk factor for ischemic stroke, especially when large and/or complex. The available data on anticoagulation or antiplatelet therapy for stroke prevention is limited and observational in nature.

**Methods:** The Patent Foramen Ovale in Cryptogenic Stroke Study (PICCS) is a substudy of the Warfarin-Aspirin Recurrent Stroke Study (WARSS). WARSS patients all had ischemic stroke within the prior 30 days. Those with cryptogenic stroke all underwent transesophageal echocardiography (TEE); they and other WARSS subjects who had TEE comprised the PICCS study group. Cardioembolic stroke or high degree carotid stenosis was exclusion criteria. Patients were randomized to 325 mg aspirin daily or warfarin adjusted to an international normalized ratio (INR) of 1.4 to 2.8; subjects were followed up to 2 years for recurrent ischemic stroke or death.

**Results:** 627 TEE studies were done with adequate visualization of the aortic arch in 516 (82%). Arch plaques were present in 65% and large plaques (≥4 mm) in 20%. Complex features (ulcerations, mobile elements) were present in 9%. The primary end point occurred in 16%. The 2-year incidence of recurrent stroke or death increased with plaque size (HR, 2.12 for large vs no plaque), especially with complex morphology (HR, 2.55). Complex morphology was also associated with earlier recurrence of events. The increased risk of recurrent stroke or death observed with large plaques was only seen in the cryptogenic stroke patients. There was no difference in event rates between the aspirin and warfarin groups. However, within the warfarin group, an INR ≥1.5 was associated with a protective effect. Major hemorrhage was low in both groups.

**Conclusions:** Large aortic plaques, especially those with complex morphology, substantially increase the risk of recurrent stroke and death. This increased risk was observed exclusively in the cryptogenic stroke patients. In the overall study group there was no difference between aspirin and warfarin treatment though subset analysis suggests protective effects for warfarin at higher INR levels.

**Reviewer's Comments:** Aortic arch plaques are a known cause of embolic stroke, especially when large (≥4 mm) and/or associated with complex elements. This study confirms a high rate of recurrent stroke or death in stroke patients who are discovered to have proximal aortic atheroma. Treatment has always been a conundrum. Surgical endarterectomy has been tried but yielded poor outcomes in small series. Because the mobile elements often contain thrombus, antiplatelet agents and anticoagulant therapy have been advocated. Unfortunately, they appeared ineffective in this study, although there was a suggestion that higher levels of anticoagulation might be protective. Statin therapy has also been recommended as the plaques are atherosclerotic in nature. Statin therapy was not routinely prescribed in this study and therefore no specific comments can be made. (Reviewer-Gregg S. Pressman, MD).

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Keywords: Aortic Atheroma, Aspirin, Warfarin, Recurrent Stroke

Print Tag: Refer to original journal article
Ranolazine Safe, Efficacious for Chronic Angina

Efficacy of Ranolazine in Patients With Chronic Angina: Observations From the Randomized, Double-Blind, Placebo-Controlled MERLIN-TIMI (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes) 36 Trial.

Wilson SR, Scirica BM, et al:
J Am Coll Cardiol 2009; 53 (April 28): 1510-1516

Ranolazine is both safe and efficacious in a diverse group of patients with chronic angina.

**Background:** Ranolazine is a relatively new anti-anginal drug with a mechanism of action that involves antagonism of the late phase of the inward sodium current. This sodium current has increased expression in the setting of myocardial ischemia and is implicated in harmful cellular sodium and calcium overload. Initial studies of ranolazine in subsets of patients with chronic angina have shown favorable results.

**Objective:** To evaluate the safety and efficacy of ranolazine in a more diverse population with chronic angina.

**Participants/Methods:** This study evaluated 3565 enrollees in the MERLIN-TIMI 36 trial, (a randomized, placebo-controlled, double-blinded study of patients presenting with non-ST-segment elevation acute coronary syndrome [ACS]). All patients had at least 1 indicator of moderate to high risk of death or recurrent ischemia. The primary end point was the first occurrence of any element of the composite of cardiovascular death, MI, or recurrent ischemia. Patients were started in-hospital on IV ranolazine (or placebo) and discharged on oral ranolazine (1000 mg twice daily) or placebo. Dose adjustments for renal insufficiency were made. Patients were on good medical therapy. Median follow-up was 350 days.

**Results:** The treatment and placebo groups were similar overall in baseline characteristics with minor differences. There were no significant differences in the number of additional anti-anginal drugs that patients took. The mean duration of chronic angina prior to study enrollment was 5.2 years. The ranolazine group had a significantly lower occurrence of the primary end point compared to the placebo group (HR, 0.86; 95% CI, 0.75 to 0.97; \( P =0.017 \)). This composite end point was due almost entirely to ranolazine's positive effect on recurrent ischemia. Positive effects on the incidence of worsening angina, severe recurrent ischemia, and the need to intensify other anti-anginal therapy were observed. There were also positive effects on exercise tolerance and the incidence of significant arrhythmias. Ranolazine had no effect on the risk of cardiovascular death or MI. Patients without a history of prior angina did not derive a benefit in terms of recurrent ischemia with the use of ranolazine. Overall safety and tolerability of ranolazine was good with a drug discontinuation rate of 8%. Significant side effects included dizziness, nausea, and constipation.

**Conclusions:** Ranolazine appears to significantly reduce the angina burden in a diverse group of patients with coronary artery disease; it has a favorable overall safety profile.

**Reviewer's Comments:** This study adds to the body of evidence indicating that ranolazine is a safe and effective drug for patients with angina. What remains to be worked out is whether this drug will become a first-line antianginal agent or reserved for angina refractory to other agents. (Reviewer-Khalid Almuti, MD).

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Keywords: Chronic Angina, Ranolazine, MERLIN-TIMI 36 Trial

Print Tag: Refer to original journal article
Dampening the increased preload during EECP by removing the calf cuffs accentuates the systolic unloading and results in enhanced contractility and decreased work of the left ventricle.

**Background:** Enhanced external counterpulsation (EECP) is a noninvasive treatment for refractory angina that uses 3 pairs of blood pressure cuffs wrapped around the calves, lower thighs, and upper thighs that inflate sequentially during diastole and deflate simultaneously just prior to systole. Invasive assessment of changes in left ventricular (LV) pressure, volume, contractility, work, and efficiency during EECP have not yet been studied.

**Objective:** To determine the direct ventricular effects of EECP.

**Design:** Cohort study.

**Participants:** 10 patients (7 men; mean age, 56 ± 8 years) with normal LV systolic function referred for diagnostic cardiac catheterization.

**Methods:** Left and right heart catheterization and coronary angiography were done. EECP was performed sequentially at 80, 160, 200, 260, and 300 mm Hg of external cuff inflation pressures. LV volume and pressure, right atrial pressure, and central aortic pressure were measured at baseline and during EECP at each of these pressure settings with 4 different cuff combinations: (1) calf cuffs only, (2) calf and lower thigh cuffs (2-cuff low), (3) lower and upper thigh cuffs (2-cuff high), and (4) all 3 cuffs.

**Results:** As cuff pressure increased, right atrial pressure, heart rate, and aortic diastolic pressure augmentation increased in all cuff combinations, most significantly with the 3-cuff setting. The increased preload from increased venous return resulted in increased left ventricular volume. Maximum positive and negative load-dependent LV contractility (dP/dt) increased. LV end-diastolic pressure (LVEDP) was reduced in the 2-cuff high and 3-cuff settings only, but more so in the 2-cuff high setting. Systolic unloading and stroke work decrease was only observed in the 2-cuff high setting. LV end-systolic and end-diastolic volumes increased with the 2- and 3-cuff settings. Myocardial efficiency (stoke work/pressure-volume area) did not change with 3-cuff setting but did decrease slightly with 2-cuff high setting.

**Conclusions:** During EECP, invasive LV hemodynamic assessment demonstrates significant augmentation of right atrial and aortic diastolic pressures. This rise in preload attenuates the drop in LV diastolic pressure resulting from systolic unloading. There was no significant effect on myocardial efficiency as the increased preload offset the afterload reduction.

**Reviewer's Comments:** During the 3-cuff setting the reduction in LVEDP was lessened by the marked increase in venous return and preload. The 2-cuff high setting (without the calf cuffs) produced less of an increase in venous return, and showed the greatest increase in maximum positive LV contractility along with the largest reduction in LVEDP and LV stroke work. The enhanced contractility and diminished LV work in this study suggest the possibility that outcomes in heart failure patients treated with EECP may be improved by using the 2-cuff high setting versus the 3-cuff setting to maximize systolic unloading while minimizing increases in preload. (Reviewer-Debra Braverman, MD).

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Keywords: EECP, LV Hemodynamics

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