Pay Attention to First-Degree AVB -- It May Not Be a Benign Finding

Long-Term Outcomes in Individuals With Prolonged PR Interval or First-Degree Atrioventricular Block.

Cheng S, Keyes MJ, et al:

JAMA 2009; 301 (June 24): 2571-2577

First-degree atrioventricular block predicts development of atrial fibrillation and need for pacemaker therapy.

**Background:** The PR interval is determined by atrial, atrioventricular node, and His-Purkinje system conduction times, with first-degree atrioventricular block (AVB) defined as >200 ms. The clinical significance of first-degree AVB in the general population is uncertain.

**Objective:** To investigate the prognosis of first-degree AVB in the community, using the Framingham Heart Study.

**Methods:** Baseline ECGs obtained from 1968 to 1974 were used to determine PR intervals. Exclusions included age <20 years, history of atrial fibrillation (AF) or pacemaker, or use of antiarrhythmics or cardiac glycosides.

**Results:** A total of 7575 subjects participated (54% women; mean age, 47 years). At baseline, 124 individuals (1.6%) had first-degree AVB with a median PR interval of 211 ms, compared to 149 ms in those without first-degree AVB. At baseline, those with first-degree AVB were older and, in general, more often had risk factors and prevalent cardiac disease. At a maximum of 20 years’ follow-up for each individual, the crude incidences of AF, pacemaker implantation, and all-cause mortality were higher in the group with first-degree AVB at baseline. With multivariate analysis, adjusted for sex, cardiovascular disease, age, heart rate, body mass index, hypertension, smoking, diabetes, and lipid profile, first-degree AVB remained a significant predictor of AF, pacemaker implantation, and all-cause mortality (hazard ratios, 2.06, 2.89, and 1.44, respectively). Adjustment for use of beta-blockers and calcium-channel blockers did not reduce the hazard ratios. Secondary analyses that adjusted for baseline long QRS interval, baseline or interim (during follow-up) development of MI, heart failure, and pacemaker implantation did not affect the main results. However, there was no relation between baseline PR interval and incidence of CAD on multivariate analysis.

**Conclusions:** Individuals with first-degree AVB have an increased risk for future AF, pacemaker implantation, and mortality compared with those without first-degree AVB.

**Reviewer's Comments:** This community-based study with long-term follow-up demonstrates the value of first-degree AVB in predicting AF, need for pacemaker, and mortality. Limitations of the study include the lack of adjustment for alcohol consumption or thyroid disease. This study does not elucidate the mechanism by which first-degree AVB predicts adverse events, nor does it define the evaluation and management of those with first-degree AVB. In addition, conditioned athletes and others may have prognostically benign first-degree AVB. In terms of mechanism, first-degree AVB might progress to higher-degrees of AVB and result in the need for a pacemaker. First-degree AVB may be associated or due to slow intra-atrial conduction, indicating atrial disease and may thereby predict AF. First-degree AVB may be a marker of associated cardiac structural or autonomic abnormalities, and therefore may predict progressive cardiac disease and mortality. Further research is clearly needed. (Reviewer-Craig M. Oliner, MD).

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Keywords: First-Degree Atrioventricular Block, Outcomes

Print Tag: Refer to original journal article
Adding B-type natriuretic peptide, a physiologic variable, to Doppler echo improves risk prediction in patients with severe but asymptomatic aortic stenosis.

**Background:** The current standard for valve replacement in aortic stenosis (AS) is to await the appearance of symptoms. However, sudden death or reduced left ventricular systolic function can occur in asymptomatic severe AS. B-type natriuretic peptide (BNP) reflects ventricular wall stress and has predictive value in many CVD states.

**Objective:** To look at combining Doppler echocardiography with BNP levels to create a new risk index for predicting outcome.

**Participants/Methods:** A development cohort of 107 patients (in France) was used to develop the index, which was then tested in a validation cohort of 107 patients (in Belgium). All subjects had moderate to severe AS, had normal ejection fraction, and were asymptomatic. Exercise testing was performed at baseline and at follow-up (every 6 to 12 months) "if indicated." Predefined end points were all-cause mortality or valve replacement due to development of symptoms or an abnormal exercise test (symptoms or abnormal blood pressure response during exercise). Follow-up was 24 months.

**Results:** In the development cohort, 62 subjects reached the primary end point. Age, sex, echocardiographic variables, and BNP were tested for association with the 24-month end point. Multivariate analysis and other statistical techniques yielded a risk score for prediction of the end point: Score=[peak velocity (m/s) x 2] + (natural logarithm of BNP x 1.5) + 1.5 (if female sex). The event rate, according to continuous score values in the combined cohort, was <10% for values <11 and >75% for values >16.

**Conclusions:** This prediction score is largely based on peak velocity across the aortic valve (indicating severity of valve disease) and BNP (indicating effect on the left ventricle). Previous work showed BNP levels correlate with severity of AS and presence of symptoms. This study suggests BNP may also help in predicting outcome. By combining echocardiography and BNP, we might better identify asymptomatic patients who need valve replacement.

**Reviewer's Comments:** This study is interesting because it suggests that adding BNP to echocardiography accurately identifies the asymptomatic AS patient at high risk for adverse events, including death. We don't want to subject patients to risks of surgery and potential complications of a prosthetic valve until benefits outweigh these liabilities. Yet, we want to minimize risks of sudden death and reduced ventricular function associated with severe AS. If this algorithm proves accurate in other populations and other centers, it should be very useful in clinical practice. It should be noted that these investigators followed guidelines of the European Society of Cardiology, which differ somewhat from the American version. In particular, the European guidelines recommend exercise testing in the assessment and follow-up of AS. In this study, many subjects underwent exercise testing, and 18 had an abnormal test as an indication for valve replacement. Because of this, the results should be interpreted with caution. (Reviewer-Gregg S. Pressman, MD).

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Keywords: Asymptomatic Aortic Stenosis, Risk Score, Prediction

Print Tag: Refer to original journal article
Benefits Seen in Young, Old After Cardiac Rehab for CAD

Comparison of Baseline Characteristics and Outcomes in Younger and Older Patients Completing Cardiac Rehabilitation.

Maniar S, Sanderson BK, Bittner V:

J Cardiopulm Rehabil Prev 2009; 29 (July-August): 220-229

Older patients involved in cardiac rehabilitation programs are more likely to have poorer functional capacity and more comorbidities at baseline, yet they are equally likely to achieve secondary prevention goals and improvement in functional status.

Background: The growing aging population combined with the improved survival rate of CAD have increased the need for comprehensive cardiac rehabilitation programs incorporating secondary prevention. However, participation in cardiac rehabilitation programs among eligible patients is exceedingly low, primarily for older patients.

Objective: To compare baseline characteristics and cardiac rehabilitation outcomes between younger and older patients.

Design: Retrospective chart review.

Participants: 685 subjects (198 women [29%]; 199 non-white [29%]) with CAD who participated in a cardiac rehabilitation program.

Methods: Detailed demographic and clinical information on each patient regarding cardiovascular risk factors, dietary habits, activity patterns, functional capacity, and perceived health status were collected, and comparisons were made between "younger" (aged <65 years) and "older" (aged ≥65 years) patients. Patients considered "young-old" (aged 65 to 74 years) and "old-old" (aged ≥75 years) were compared in subanalyses.

Results: At baseline, older patients had poorer functional capacity by 6-minute walk test, higher blood pressures, and more comorbidities (all \( P < 0.05 \)) but had less depression, better lipid profiles, lower body mass indices, and lower hemoglobin A\(_1c\) levels (all \( P < 0.05 \)), as compared to younger patients. In response to cardiac rehabilitation, improvement in all measures (\( P < 0.05 \)), except HDL cholesterol and diastolic blood pressure, occurred in older patients. Additionally, improvement in all measures (\( P < 0.05 \)), except HDL cholesterol, occurred in younger patients. Both young-old and old-old patients showed improvements in most outcomes by cardiac rehabilitation completion without significant differences by age group. Age was not a significant predictor of attaining secondary prevention targets at the conclusion of cardiac rehabilitation.

Conclusions: Upon entering cardiac rehabilitation, older patients have more comorbidities but fewer cardiac risk factors than do younger patients. All age groups studied yielded significant improvement from cardiac rehabilitation.

Reviewer's Comments: This study denotes the greatest older cohort with sizeable representation of non-white and female patients that has been analyzed for baseline characteristics and secondary prevention outcomes of cardiac rehabilitation. The generally superior risk factor profile of the older patients probably indicates survival bias. Future research is warranted to cultivate strategies to boost cardiac rehabilitation participation among older adults and to further study benefits of such programs intended to lessen the individual and societal burden of disability due to CAD among our aging population. (Reviewer-Debra L. Braverman, MD).

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Keywords: Baseline Characteristics, Outcomes, Younger vs Older Patients

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Exercise Benefits Patients Undergoing CRT

Maximizing Patient Benefit From Cardiac Resynchronization Therapy With the Addition of Structured Exercise Training: A Randomized Controlled Study.

Patwala AY, Woods PR, et al:

J Am Coll Cardiol 2009; 53 (June 23): 2332-2339

Exercise training under physician-supervision advances the benefits of cardiac resynchronization therapy.

Background: Cardiac resynchronization therapy (CRT) has been shown to improve exercise capacity, NYHA functional class, peak oxygen consumption (VO₂), quality of life (QOL), and possibly mortality. Exercise training has been found to improve exercise capacity, VO₂, QOL, and mortality in patients with chronic heart failure, although most trials focused on patients with mild disease. It is suspected that the improvement in VO₂ is due to improvements in cardiac output and peripheral skeletal muscle extraction of oxygen. It is unclear whether exercise training could benefit patients with more severe heart failure undergoing CRT.

Objective: To assess if patients undergoing CRT have additional improvement in VO₂ when they undergo exercise training.

Participants/Methods: NYHA class III and IV patients on stable, optimal medical therapy undergoing CRT were asked to participate if they had no non-cardiac physical limitations. Patients underwent an echocardiogram, QOL assessment by standardized questionnaire, and measurement of skeletal muscle torque at baseline and at 3 and 6 months after CRT. After the 3-month visit, patients were randomized. The exercise group underwent a physician-guided exercise regimen of three 30-minute sessions per week. Each session had 10 minutes of walking, 10 minutes of cycling, and 10 minutes of walking with escalating targets of peak heart rate from 80% to 90%. The control group had no recommended exercise protocol.

Results: 50 patients were randomized equally to the 2 groups. At 3 months, there was a significant improvement in VO₂, NYHA, exercise duration, cardiac volumes, ejection fraction, and QOL with CRT. At 6 months (3 months post-randomization), the exercise group had significantly better VO₂, NYHA, exercise duration, and QOL than did the control group. The exercise group also had significantly better measures of skeletal muscle strength.

Conclusions: Exercise training supplements the clinical benefits of CRT.

Reviewer's Comments: Benefits of exercise are well documented. This interesting study suggests a multidisciplinary approach to the treatment of heart failure, specifically encouraging exercise, may be beneficial with broad-reaching effects. Further study is necessary to evaluate appropriate duration and frequency of weekly exercise and, of practical necessity, potential benefits and risks of unsupervised exercise therapy. One limitation of the study is the lack of a non-CRT control group. It is unclear whether matched control patients who did not undergo CRT would have had similar benefits with exercise training. (Reviewer-Sumeet K. Mainigi, MD).

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Keywords: Cardiac Resynchronization Therapy, Biventricular Pacing, Exercise, Heart Failure

Print Tag: Refer to original journal article
This study illustrates the possible optimal international normalized ratio that physicians should try to achieve when treating patients with a mechanical valve prosthesis, atrial fibrillation, or myocardial infarction.

**Background:** Oral anticoagulant therapy with vitamin K antagonists has been effective in both primary and secondary prevention of arterial thromboembolism. However, the increased risk of hemorrhage still remains a significant drawback to this therapy and is associated with the intensity of anticoagulation and other patient characteristics such as age and sex. Finding the optimal intensity at which the overall incidence rate of both bleeding and thromboembolic events is minimized would improve the safety of oral anticoagulant treatment.

**Participants/Methods:** All patients visiting the Leiden Anticoagulation Clinic, a regional clinic in the Netherlands, with mechanical heart valve prostheses, atrial fibrillation (AF), or MI from 1994 to 1998 were evaluated. Therefore, 4202 patients (total of 7788 patient-years) were enrolled. Untoward events were defined as major thromboembolism and major hemorrhage. Optimal intensity of oral anticoagulation was defined as the international normalized ratio (INR) level that provided the lowest overall incidence of untoward events. This allowed for calculating intensity-specific incidence rates of untoward events to assess the optimal intensity per indication of treatment.

**Results:** There were 3226 hospital admissions reported; 306 were due to an untoward event. Incidence rates of untoward events was approximately 4% per year for all indications: 4.3 for patients with mechanical heart valve prostheses, 4.3 for patients with AF, and 3.6 per year for patients treated after an MI. U-shaped curves subsequently demonstrated that the optimal intensity of anticoagulation for patients with mechanical heart valve prostheses was an INR of 2.5 to 2.9; for patients with AF, an INR of 3.0 to 3.4; and for patients after MI, an INR of 3.5 to 3.9.

**Conclusions:** This study suggests that for patients on oral anticoagulation with vitamin K antagonists, target INRs of 3.0 for patients with mechanical heart valve prostheses and AF and 3.5 after MI may be the goal of therapy.

**Reviewer’s Comments:** Oral anticoagulation with vitamin K antagonists has been administered to patients for more than half a century for prevention of thromboembolism. However, there continues to be serious risks to this treatment, especially serious life-threatening hemorrhage at a higher intensity of treatment and thromboembolism at a lower intensity of treatment. This study illustrates the possible optimal INR that physicians should try to achieve when treating patients with a mechanical valve prosthesis, AF, or post-MI. This optimal INR level may significantly maintain the best balance between thromboembolism versus the risk of hemorrhage. Since the study was done in a regular anticoagulation clinic, these results may be applied in regular medical practices. (Reviewer-Suraj Maraj, MD).

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Keywords: Oral Anticoagulant Therapy, Arterial Thrombosis, Mechanical Heart Valve Prostheses, Atrial Fibrillation, Myocardial Infarction

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Statins Can Cause Coronary Artery Atherosclerotic Plaque Regression

Effect of Intensive Statin Therapy on Regression of Coronary Atherosclerosis in Patients With Acute Coronary Syndrome: A Multicenter Randomized Trial Evaluated by Volumetric Intravascular Ultrasound Using Pitavastatin Versus Atorvastatin (JAPAN-ACS Study).
Hiro T, Kimura T, et al:
J Am Coll Cardiol 2009; 54 (July 21): 293-302

Treatment with pitavastatin or atorvastatin in patients with acute coronary syndrome can significantly reduce atherosclerotic plaque burden and cause reverse remodeling of coronary blood vessels.

Background: There is strong evidence that statin drugs have significant effects in decreasing mortality and morbidity for patients with atherosclerotic heart disease. These effects are largely attributed to atherosclerotic plaque stabilization. Some small studies using intravascular ultrasound (IVUS) have suggested that statins may actually cause plaque regression.

Objective: To assess the effect of atorvastatin versus pitavastatin on the regression of non-culprit vessel coronary plaque volume in patients presenting with acute coronary syndrome (ACS).

Design: Prospective, randomized open-label study.

Methods: All patients had angioplasty for ACS. Those with readable IVUS studies of non-culprit vessels at the time of angioplasty and at 8- to 12-month follow-up were included. Post-angioplasty, patients were randomized to either pitavastatin 4 mg or atorvastatin 20 mg daily. The primary end point was the percentage change in the vessel's plaque volume (PV).

Results: A total of 125 patients were included in the pitavastatin group and 127 in the atorvastatin group. Baseline characteristics were similar in the 2 groups. Of patients, 64% had ST elevation MI as the presenting ACS. Participants were predominantly male (82%), and 29% were diabetic. Patients in both groups had significant and similar decreases in LDL cholesterol levels. Both groups had significant and similar regression in coronary PV (-17% overall). This regression caused negative remodeling of involved coronary vessels, leading to significant lumen size enlargement. Of note, there was no correlation between LDL levels at baseline or on treatment with the percentage change in PV. There were no significant differences in adverse effects between the 2 study drugs, with very low drug discontinuation rates. The rate of major adverse cardiovascular events was also similar for both drugs.

Conclusions: Treatment with pitavastatin or atorvastatin in patients with ACS can significantly reduce atherosclerotic plaque burden and cause reverse remodeling of coronary blood vessels.

Reviewer’s Comments: This study provides more evidence that statin drugs should be given to all patients presenting with an ACS unless a contraindication exists. To date, statin drugs seem to be somewhat of a miracle drug class, with ever-expanding evidence of benefit and very modest potential harm. (Reviewer-Khalid Almuti, MD).

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Keywords: Statins, Coronary Plaque, Atherosclerosis, Acute Coronary Syndrome, Effects

Print Tag: Refer to original journal article
Accurate Dx, Reduced Radiation in CAD Using Prospectively Gated CTA

Diagnostic Accuracy of Coronary Computed Tomography Angiography: A Comparison Between Prospective and Retrospective Electrocardiogram Triggering.

Pontone G, Andreini D, et al:

J Am Coll Cardiol 2009; 54 (July 21): 346-355

Prospectively gated coronary CT angiography offers accurate diagnosis of CAD with a significantly reduced radiation dosage.

**Background:** Cardiac CT angiography (CTA) is increasing in popularity for assessing coronary arteries noninvasively. However, the high radiation dosage from retrospectively gated CTA is a concern.

**Objective:** To compare the diagnostic accuracy and radiation exposure of retrospectively gated CTA with prospectively gated CTA.

**Participants/Methods:** 180 patients were randomly selected from a cohort scheduled to undergo invasive coronary angiography for suspected CAD. Eighty-four patients eventually underwent prospectively gated CTA, and 82 underwent retrospective gating. Significant stenosis was defined as luminal narrowing >50%, and invasive coronary angiography was used as the gold standard.

**Results:** Both groups were fairly homogenous at baseline. Overall evaluability was slightly higher for non-stented segments with retrospective gating (97% vs 96%). This was due to lower artifacts in non-stented segments with retrospective gating (3% vs 8%). However, blooming artifacts were higher and motion artifacts lower with retrospective gating. The overall image quality was slightly better with retrospective gating (excellent quality in 95% vs 92%) in non-stented segments but was no different in stented segments. In a per-segment-based model, the sensitivity, specificity, positive-predictive value, and accuracy were higher with retrospective gating (94%, 94%, 86%, and 94%, respectively). However, the sensitivity in stented segments was higher with prospective gating (93% vs 77%). On a per-patient-based analysis, there were no differences in sensitivity, specificity, negative- or positive-predictive values, and accuracies between groups. The radiation dosage was significantly lower with prospective gating (5.7 mSv vs 20.5 mSv) and was similar to invasive coronary angiography (6.3 mSv).

**Conclusions:** On a per-patient-based analysis, prospectively gated CTA accurately detected CAD with a radiation dose comparable to invasive coronary angiography, albeit with slightly lower diagnostic performance when compared to retrospective gating.

**Reviewer's Comments:** The results of this study are slightly different from a recent study comparing retrospective versus prospective gating that showed similar coronary assessibility, sensitivity, and specificity between the 2 modalities (J Am Coll Cardiol 2008;52:1450-1455). Despite lower sensitivity, specificity, positive-predictive value, accuracy, and assessibility of prospective CTA when using a per-segment analysis, there were no differences in these values when using a more clinically useful per-patient-based approach. There was a very significant 72% reduction in radiation dosage with prospective gating, making this modality more attractive for routine clinical use. In fact, sensitivity for evaluation of stents was higher with prospective gating due to fewer blooming artifacts with this technique. However, higher motion artifacts due to heart rate variability could be a significant limitation of this modality. (Reviewer-Anoop C. Parameswaran, MD).

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Keywords: Coronary CT Angiography, Accuracy, Evaluability, Prospective Gating

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Among patients with an acute coronary syndrome, PCI-related MI occurs among high-risk patients with diffuse disease and a high plaque burden.

**Background:** Although MI in the setting of PCI has been associated with higher long-term mortality, it is not clear whether the relationship is always causative. Small MIs caused by distal embolization of plaque during otherwise "successful" PCIs are the result of greater plaque burden, diffuse disease, and a heightened inflammatory state, and not the procedure itself. Despite this, periprocedural MIs and spontaneous MIs occurring due to plaque rupture are combined as outcomes in clinical studies.

**Objective:** To determine the relative prognostic significance of periprocedural MI versus spontaneous MI among patients with acute coronary syndrome (ACS) treated with PCI.

**Participants/Methods:** Patients with non-ST-segment ACS enrolled in the multicenter ACUITY trial and treated with PCI were included. Creatine phosphokinase MB (CK-MB) measurements were made every 8 hours in the first 24 hours post-PCI. MI was defined as a CK-MB elevation >3 x the upper limit of normal (ULN). Periprocedural MI was any MI occurring the day of or day after the procedure. Any MI afterward was considered spontaneous. Follow-up duration was 1 year.

**Results:** Of 7773 patients in the ACUITY trial who underwent PCI, 6.0% developed periprocedural MI and 2.6% developed spontaneous MI. There was no significant difference in the incidence of Q-wave MI between groups (approximately 18%). There was a greater prevalence of diabetes in the spontaneous MI group. Both groups were associated with a higher likelihood of prior MI or revascularization and a higher TIMI risk score. Compared to patients without MI, both groups of MI patients had a significantly higher mortality at 1 year (no MI, 2.6%; periprocedural MI, 6.0%; spontaneous MI, 16%). The mortality difference between the 2 MI groups was also statistically significant. There was no statistically significant difference in mortality among patients with Q-wave MIs (periprocedural, 27%; spontaneous, 17%; \( P = 0.22 \)). A multivariate analysis adjusting for baseline variables indicated that spontaneous MI was the strongest indicator of subsequent mortality. Periprocedural MI was not found to be significantly related to later mortality.

**Reviewer's Comments:** Similar to prior studies, this study demonstrates the association of periprocedural MI with higher-risk patients, greater plaque burden, and lesion complexity. Although there was an increase in subsequent mortality among patients with periprocedural MI, it was not found to be an independent predictor of mortality. Mortality among patients with periprocedural MI is most likely related to the patients' disease process and not the small degree of myonecrosis detected by cardiac enzyme elevation. This is in contrast to spontaneous MI, which was found to be the strongest independent predictor of mortality among this group of ACS patients. The results of this study challenge the notion that all periprocedural MIs detected with a low CK-MB threshold have a causative impact on mortality. (Reviewer-Parul B. Patel, MD).

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Keywords: Percutaneous Coronary Intervention, Periprocedural, Myocardial Infarction, Acute Coronary Syndromes

Print Tag: Refer to original journal article
The results of this study found no benefit to closure of an incidentally found patent foramen ovale during cardiothoracic surgery.

**Background:** The relationship between patent foramen ovale (PFO) and cryptogenic stroke remains unclear. Furthermore, what to do with an incidentally diagnosed PFO in an asymptomatic patient is not known. Intraoperative transesophageal echocardiography (TEE) finds incidental PFOs in approximately one fourth of patients undergoing cardiothoracic surgery.

**Objective:** To examine the prevalence of intraoperatively diagnosed PFO in cardiac surgery patients and to determine whether perioperative outcomes and long-term survival differ between patients with PFOs and those without, as well as between patients with PFOs not repaired versus those with PFOs repaired intraoperatively.

**Methods:** The authors reviewed intraoperative TEE reports from patients undergoing cardiothoracic surgery between 1995 and 2006 at the Cleveland Clinic. Postoperative stroke and all-cause hospital deaths were primary outcome measures. Length of stay in the hospital, length of stay in ICU, total time spent on cardiopulmonary bypass and long-term survival were secondary outcome measures.

**Results:** In the final dataset of 14,165 patients with TEE data available, 13,092 were included; 1046 patients were excluded because of previous PFO or atrial septal defect diagnosis. A total of 2277 patients (17%) had PFOs discovered intraoperatively; of these, 639 had their PFO repaired intraoperatively. Of note, risk factors for stroke were similar in patients with and without PFOs. Patients with PFOs demonstrated similar rates of in-hospital death and postoperative stroke compared to those without PFOs. Patients with repaired PFOs had a 2.5 times greater odds of postoperative stroke compared to those with unrepaired PFOs. Long-term survival was not different between patients with PFOs and those without, nor between patients with PFOs not repaired versus those with PFOs repaired. Including the 1046 patients excluded because of prior diagnosis of PFO or atrial septal defect, the prevalence of PFO in this population was approximately 24%, which is in line with prior autopsy studies.

**Conclusions:** PFOs discovered incidentally during intraoperative TEE for cardiothoracic surgery have a benign short-term and long-term clinical course. There is no benefit from closure on short-term postoperative outcomes or long-term survival. Based on this study, the finding that PFO repair may increase postoperative stroke raises the question as to whether routine surgical closure is appropriate.

**Reviewer's Comments:** This study sheds light on the question that many cardiologists encounter: what should be done with a PFO? The role of PFO and cryptogenic stroke remains unclear. The advantage of repairing a PFO intraoperatively, when found incidentally on TEE, was not known. The present study suggests a benign nature to incidentally found PFOs and suggests that closure may in fact be detrimental. Further investigation will be necessary to determine whether subgroups of patients may benefit from PFO closure to prevent strokes long term. (Reviewer-Vincent M. Figueredo, MD).

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Keywords: Patent Foramen Ovale, Cardiothoracic Surgery, Stroke

Print Tag: Refer to original journal article
Patients with established CAD are candidates for antiplatelet therapy; aspirin is the most commonly used agent.

**Background:** The implantation of coronary stents has become a frequent mode of therapy for CAD requiring intervention. Placement of both bare-metal stents (BMSs) and drug-eluting stents (DESs) require dual-antiplatelet therapy (DAP) for at least 1 month and with a DES for at least 1 year or longer. Anticoagulation impacts an ever-increasing portion of the cardiology patient population for stroke prevention in disease processes such as atrial fibrillation, among other diagnoses. Both of these therapeutic regimens carry associated risks, especially bleeding. When the 2 regimens intersect, the risk is even higher.

**Objective:** To review the current literature. **Discussion:** Patients with established CAD are candidates for antiplatelet therapy. Aspirin (ASA) is the most commonly used agent. As the dose of ASA increases, the risk of bleeding increases. Data suggest that a lower dose of ASA (≤162 mg/day) is as effective as a higher dose and carries less risk of bleeding. The benefit of ASA outweighs the risk at lower doses. DAP with ASA and a thienopyridine is indicated in patients with acute coronary syndrome, following PCI with stent implantation and for stroke treatment and prevention. The risk of bleeding increases with the additional platelet inhibition. The risk of bleeding appears to be less, with no loss of effectiveness if low-dose ASA is combined with the thienopyridine. There is no definitive recommendation for duration of therapy. Warfarin is indicated in patients with atrial fibrillation, left ventricular thrombus, severe left ventricular dysfunction, mechanical heart valves, deep venous thrombosis, and pulmonary embolism. There is a recognized risk of bleeding with warfarin therapy. For many of these patients, warfarin is not an adequate substitute for ASA and a thienopyridine. This is especially true for prevention of stent thrombosis. In this patient population, 3 drugs are required. This further increases the risk of bleeding. Recommendations for this patient population include the following: The dose of ASA should be kept as low as possible. Clopidogrel should be given at the standard dose. Warfarin should be closely monitored with a target international normalized ratio of 2.0 to 2.5. A proton pump inhibitor should be considered, with the possible exception of omeprazole. If bleeding occurs, the best drug to discontinue is ASA, maintaining the other 2 agents if possible. For patients receiving warfarin and being considered for PCI, the need for 3 drugs and the duration of therapy should be considered when choosing a stent. A BMS may be the better choice for many patients to shorten the duration of triple-drug therapy and to narrow the risk exposure.

**Reviewer's Comments:** The authors reviewed the current literature on combining antiplatelet and anticoagulant therapies, and they provided an excellent white paper on this topic. (Reviewer-D. Lynn Morris, MD).

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Keywords: Antiplatelets, Anticoagulants, Stents

Print Tag: Refer to original journal article
Treatment with valsartan is not associated with a reduction in the incidence of recurrent atrial fibrillation.

**Background:** Studies have shown that angiotensin II-receptor blockers (ARBs) can influence atrial structural and electrical remodeling, and some clinical studies suggest that they may prevent atrial fibrillation (AF).

**Objective:** To examine whether valsartan therapy can reduce recurrence of AF.

**Design/Methods:** GISSI-AF was a large randomized, prospective placebo-controlled multicenter trial to test whether valsartan could reduce the recurrence of AF. "Patients who were in sinus rhythm but had had either ≥2 documented episodes of AF in the previous 6 months or successful cardioversion for AF in the previous 2 weeks were enrolled." To be eligible, patients also had to have underlying cardiovascular disease, heart failure or LVEF <40%, history of stroke or PAD, CAD, diabetes, hypertension, or left atrial enlargement. Patients were excluded if they had contraindications to ARBs, recent MI in the past 6 weeks, CABG, or PCI. Patients were randomly assigned to receive valsartan or placebo. They were allowed to continue all previously prescribed medications including amiodarone, beta-blockers, and ACE inhibitors. The authors stated that, "the 2 primary end points were the time to a first recurrence of AF and the proportion of patients who had >1 recurrence of AF over the course of 1 year."

**Results:** 1442 patients were enrolled. AF recurred in 51.4% and 52.1% of the valsartan and placebo groups, respectively (adjusted hazard ratio, 0.97; 96% CI, 0.83 to 1.14; \( P =0.73 \)). More than 1 episode of AF occurred in 26.9% of the valsartan group and in 27.9% of the placebo group (adjusted odds ratio, 0.89; 99% CI, 0.64 to 1.23; \( P =0.34 \)). The results were similar in all predefined subgroups of patients, including those who were not receiving ACE inhibitors.

**Conclusions:** Treatment with valsartan was not associated with a reduction in the incidence of recurrent AF.

**Reviewer's Comments:** In my opinion, this was a very well-conducted study. The GISSI-AF trial was a study of secondary prevention of AF and showed that addition of valsartan to established therapies of AF did not reduce the first recurrence or multiple recurrences of AF. It may be possible that ARBs show efficacy in primary prevention of AF rather than secondary prevention, as these drugs may prevent but not reverse development of atrial structural and electrical remodeling. The results of this study are important, as they do not support adjunctive use of valsartan for prevention of AF in patients who have hypertension, have required recent cardioversion, and are receiving established therapies for prevention of AF. Future studies are needed to determine whether blockade of the renin-angiotensin-aldosterone system plays an important role in the primary or secondary prevention of AF. (Reviewer-Sahil Mehta, MD).
The risk of sudden cardiac death in hypertrophic cardiomyopathy patients is unpredictable, even after an initial episode.

**Background:** Certain patients with hypertrophic cardiomyopathy (HCM) have an increased risk of sudden cardiac death (SCD). The timing of SCD events is highly unpredictable. Despite poor data, survivors of an initial episode of aborted SCD (whether due to resuscitation or defibrillator shock) are generally considered to have a malignant disease course with poor short- to mid-term survival.

**Objective:** To define the long-term natural history and survival in HCM patients who survive an initial episode of SCD.

**Design/Methods:** Retrospective review of 916 HCM patient records at a single heart hospital. Of these, 39 survived an initial episode of SCD and were included in the study, with the entry date being the date of the initial SCD episode. Sustained ventricular tachycardia (VT) or ventricular fibrillation was documented in 21 patients. The other 18 patients had appropriate defibrillator (ICD) shocks for life-threatening arrhythmias. The status of each patient was assessed as of May 2008.

**Results:** Patients ranged in age from 8 to 68 years (mean, 34 years) at the time of the initial SCD episode. Mean left ventricular wall thickness was 25 mm. The majority had mild or no heart failure symptoms at study entry. ICDs were implanted in 37 patients at or after study entry. Of 39 patients included, 19 had subsequent arrhythmic events (48 total events) that led to ICD shocks or cardiac arrest. The time from the initial SCD event to the subsequent episode was highly variable, ranging from 11 days to 21 years (mean, 3.2 years). Thirty-two patients (82%) survived 1.7 to 30.0 years (mean, 9.4 years) from study entry. Four patients survived >20 years. Fifteen of 32 survivors (47%) experienced no further major arrhythmias. The other 17 patients had 1 to 7 further events. Survivor groups with and without further events did not differ from each other in clinical or demographic parameters. Seven patients died during follow-up an average of 8 years after study entry, with only 1 death attributed to SCD. This resulted in 88% of enrollees being free of HCM-related death over the follow-up period, and an annual HCM-related mortality of 1.4% (2.0% overall mortality). The rate of HCM-related death or appropriate ICD shocks was 6.1% per year.

**Conclusions:** Findings in these high-risk HCM patients suggest that the risk of subsequent SCD episodes and appropriate ICD shocks is highly variable and unpredictable. Overall mortality is not as dismal as previously thought, and may in fact be similar to overall mortality in the general population of patients with HCM.

**Reviewer’s Comments:** These are interesting findings in a substantial number of patients, suggesting that many HCM patients who survive SCD may have a long life expectancy. These findings dismiss the notion that such SCD events herald the beginning of the end for survivors of such events. (Reviewer-Khalid Almuti, MD).

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**Keywords:** Hypertrophic Cardiomyopathy, Sudden Cardiac Death, Survival

**Print Tag:** Refer to original journal article
Cardiovascular and respiratory rhythms closely track musical rhythms and dynamics.

**Background:** Previous work has suggested that cardiovascular and respiratory responses to music are related to tempo, and they occur regardless of musical preference or training. Mayer waves are spontaneous cycles of blood pressure variation that occur with a 10-second periodicity (6 cycles/minute) as a result of interaction between vagal and sympathetic influences.

**Objective:** To look at autonomic responses to different types of classical music, and to evaluate whether musical phrases at 6 cycles/minute could entrain such responses.

**Participants/Methods:** 24 healthy young subjects, half of whom were trained singers, were studied. Various musical tracks were presented in random order ranging from "intellectual" (Bach) to "emotional" (Puccini and Verdi arias, Beethoven's 9th Symphony), as well as a 2-minute silence. Skin temperature (a measure of vasoconstriction), systolic and diastolic pressure, middle cerebral artery blood flow, respiration, and heart rate were recorded. Musical profiles were converted to a low-frequency signal proportional to the audio amplitude and compared with individual physiologic responses and group averages.

**Results:** Consistent responses were noted within individuals and for the group, with no differences between musicians and non-musicians. Crescendos produced skin vasoconstriction, increases in heart rate and blood pressure, and deepening of respiration. The Bach and the 2-minute silence produced a general pattern of relaxation. Coherence between cardiovascular responses and rhythmic phrases with an approximate 10-second periodicity (Verdi aria "Va pensiero") was high throughout, indicating entrainment at this frequency.

**Conclusions:** Cardiovascular and respiratory fluctuations mirror musical variation, particularly during crescendos. Specific musical phrases with a frequency of 6 cycles/minute appear to entrain cardiovascular rhythms. The authors suggest that emotional responses to music may result from induced physiologic changes rather than the usual paradigm of emotional responses causing those changes. They further suggest that the ability of music to produce physiologic changes may contribute to the usefulness of music as a therapeutic tool.

**Reviewer's Comments:** This study adds to our knowledge of music as it affects the brain and autonomic nervous system. The neurologist Oliver Sacks has authored many popular books on the diverse and important interactions of music and the brain. These include recovery of language and ambulation after stroke or physical injury. Apparently, music is "hard wired" in the brain with extensive and redundant connections throughout. The authors' suggestion that physiologic entrainment precedes, and may actually produce, emotional response is intriguing. (Reviewer-Gregg S. Pressman, MD).

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Keywords: Music, Cardiovascular Rhythms, Entrainment

Print Tag: Refer to original journal article
Heart Failure Prognosis Improved With Treadmill Use

Importance of Treadmill Exercise Time as an Initial Prognostic Screening Tool in Patients With Systolic Left Ventricular Dysfunction.

Hsich E, Gorodeski EZ, et al:

Circulation 2009; 119 (June 30): 3189-3197

Treadmill exercise time adds prognostic value to maximal oxygen consumption in patients with systolic heart failure.

Background: Peak oxygen consumption (VO2) is a powerful predictor of mortality in patients with heart failure due to systolic dysfunction, and is commonly used to make decisions about transplantation. However, VO2 is determined by cardiopulmonary stress testing, a procedure not available in all hospitals.

Objective: To evaluate treadmill exercise time (TET) to see how well it predicts mortality in this population and whether it adds incremental prognostic value to that of VO2.

Participants/Methods: 2231 consecutive patients with an ejection fraction <40% who underwent cardiopulmonary stress testing at Cleveland Clinic were studied. Symptom-limited cardiopulmonary stress testing was performed using a modified Naughton protocol (increase of 1 metabolic equivalent every 2 minutes). Primary end points were all-cause death and a combination of all-cause death with United Network for Organ Sharing (UNOS) status 1 heart transplantation class (the sickest patients awaiting transplant). Mean follow-up was 5 years.

Results: In both men and women, those in the lowest quartile of TET had worse survival than those in the highest quartile. After multivariate adjustment for age, sex, presence of CAD, and VO2, TET remained associated with both primary end points. For each 1-minute decrease in exercise time, there was a 7% increased risk of death (hazard ratio, 1.07; 95% CI, 1.02 to 1.12; P =0.004). These associations were rigorously tested for bias and remained significant. Even among subjects with VO2 >14 mL/kg per minute (a marker of lower risk), those who had a lower TET had substantially worse outcomes.

Conclusions: Exercise time adds independent prognostic value in the assessment of heart failure patients with systolic dysfunction, even accounting for VO2. While TET cannot replace formal cardiopulmonary exercise testing in determining the need for transplantation, it may be a reasonable screening tool.

Reviewer’s Comments: We live in an age of convenience and inactivity. People are not only exercising less, they and their physicians are resorting to pharmacologic stress testing more and more. This article reminds us that there is tremendous prognostic value in treadmill exercise time, not only in the heart failure patient, as demonstrated here, but also in all patients with known or suspected cardiac disease. TET also has the virtue of being a direct measurement, and is not subject to errors of processing and data manipulation. (Reviewer-Gregg S. Pressman, MD).

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Keywords: Treadmill Exercise Time, Oxygen Consumption, Systolic Dysfunction, Prognosis

Print Tag: Refer to original journal article
Sedentary lifestyle leads to disuse of weight-bearing lower extremity muscles in cardiac patients, resulting in weakness and predisposing to loss of functional independence.

**Background:** Cardiac rehabilitation traditionally focuses on endurance training. However, daily activities of cardiac patients are limited, not only by reduced endurance capacity, but also by strength deficits.

**Objective:** To compare muscular strength in cardiac patients and healthy controls, to analyze the influence of age on muscular strength, and to assess the relationship between sports history and muscular strength in cardiac patients.

**Design:** Observational case-controlled study.

**Participants:** 638 cardiac patients (540 male, 98 female; 48.7% after MI, 43.5% with CAD, and 7.8% with left ventricular hypertrophy, cardiomyopathy, and congestive heart failure), who participated in a 3-week rehabilitation program focusing on endurance and strength training. In total, 961 healthy subjects (414 male, 547 female) who had no experience in regular strength training for comparison.

**Methods:** Maximal isometric torques (MIT) were obtained from bilateral elbow flexors and knee extensors at a joint angle of 90°. Measurements were taken in cardiac patients within the last 4 days of the 3-week rehabilitation program. Subjects were divided into 3 groups according to their athletic background: (1) those who never participated (20.7%); (2) those who participated in the past but not in the last 2 years (43.1%); and (3) those who participated in regular sports activities, such as jogging, soccer, or cycling (36.2%). Age-related subgroup analysis was performed.

**Results:** In both subjects and controls, men had significantly higher MIT than did women, and there was a significant age-related reduction in MIT. Arm flexor muscle strength was not different in controls versus cardiac patients, regardless of their sports history. In contrast, leg extensor strength was significantly influenced by cardiac status and sports history. Highest values were measured in controls (male, 167 ± 16 Nm; female, 93 ± 17 Nm), while lowest values were measured in the sedentary cardiac rehabilitation patients (male, 148 ± 18 Nm; female, 82 ± 25 Nm).

**Conclusions:** The weakness of lower extremity muscles in cardiac patients is not due to pathological skeletal muscle metabolism, but it is a consequence of disuse.

**Reviewer’s Comments:** In this study, the finding that arm flexor strength is similar in both cardiac patients and controls indicates that there is nothing physiologically abnormal about skeletal muscle in cardiac disease, and the leg extensor weakness seen in cardiac patients is from selective disuse in a sedentary lifestyle. Individuals have difficulties in functional tasks beneath a critical level of muscular strength. This is exaggerated with age, and may lead to functional dependence. Strengthening of skeletal muscles, especially weight-bearing muscles, and in older patients in particular, has to be considered as a part of cardiac rehabilitation in addition to standard endurance training, in order to maximize the overall functional benefits of such programs. (Reviewer-Debra L. Braverman, MD).

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Keywords: Cardiac Rehabilitation, Skeletal Muscle Strength, Age, Sports History

Print Tag: Refer to original journal article
More Benefits Likely With High-Dose NAC for CIN Patients

*N-acetylcysteine Versus Ascorbic Acid for Preventing Contrast-Induced Nephropathy in Patients With Renal Insufficiency Undergoing Coronary Angiography NASPI Study--A Prospective Randomized Controlled Trial.*

Jo SH, Koo BK, et al:

Am Heart J 2009; 157 (March): 576-583

High-dose *N*-acetylcysteine seems more beneficial than ascorbic acid in preventing contrast-induced nephropathy in high-risk patients.

**Background:** Contrast-induced nephropathy (CIN) is known to be a leading cause of hospital-acquired renal failure and affects mortality and morbidity. Both *N*-acetylcysteine (NAC) and ascorbic acid have been shown to reduce CIN occurrence. There are no studies evaluating the relative efficacies of these 2 agents.

**Objective:** To compare the efficacy of NAC and ascorbic acid for CIN prevention in patients with renal insufficiency.

**Design/Methods:** The authors conducted a prospective randomized controlled trial enrolling 212 patients with preexisting renal impairment (basal creatinine clearance ≤60 mL/minute and/or serum creatinine (SCr) level of ≥1.1 mg/dL) who were randomized to have either high-dose NAC (1200 mg orally twice a day before and on the day of coronary catheterization) or ascorbic acid (3 g and 2 g orally before, and 2 g twice after coronary catheterization with a 12-hour interval). The authors stated that "the primary end point was the maximum increase of SCr level, and the secondary end point was the incidence of CIN defined as relative increase in baseline SCr level of ≥25% and/or an absolute increase of ≥0.5 mg/dL within 48 hours after contrast administration.” Patients with cardiogenic shock, acute renal failure, prior contrast use in last 7 days, and the use of NSAIDs and metformin within 48 hours were excluded. At 6 months, SCr level was measured in both study groups to reassess renal function.

**Results:** The maximum increase of SCr level was significantly lower in the NAC group than in the ascorbic acid group, and this result was statistically significant. Patients with diabetes or those who had received a high dose of contrast media experienced a statistically significantly lower rise of SCr level with NAC than ascorbic acid. The incidence of CIN, the secondary end point, tended to be in favor of NAC rather than ascorbic acid; however, the result was not statistically significant. There was no difference in the length of hospital stay in both groups. Among diabetic patients, NAC significantly lowered the CIN rate compared to ascorbic acid (0% vs 12.5%, respectively).

**Conclusions:** High-dose NAC seems more beneficial than ascorbic acid in preventing CIN in patients, especially diabetic patients, with renal insufficiency undergoing coronary angiography.

**Reviewer’s Comments:** In my opinion, this is a very well-conducted study. Some limitations include: no control group, small length of observation of 48 hours, and small number of patients enrolled, thus a low power. This was the first study to compare NAC and ascorbic acid head-to-head for their relative efficacy in preventing CIN. Future studies need to be conducted in much larger populations at high risk with long-term follow-up to fully assess and compare long-term effects of the 2 agents. (Reviewer-Sahil Mehta, MD).

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Keywords: Contrast-Induced Nephropathy, *N*-acetylcysteine, Ascorbic Acid, Renal Insufficiency

Print Tag: Refer to original journal article
While ACE inhibitors as a class do not appear to be independently associated with dementia risk or cognitive decline in older hypertensive adults, there may be within-class differences in regard to these outcomes.

**Background:** Hypertension (HTN) is a risk factor for both Alzheimer disease and vascular dementia. Epidemiological data have shown an association between use of anti-HTN medications and a lower risk of dementia. Animal studies suggest that centrally active ACE inhibitors (those that cross the blood-brain barrier) may have a protective effect against dementia in addition to HTN control.

**Participants/Methods:** Participants in the Cardiovascular Health Study Cognition Substudy with treated HTN (n=1054; mean age, 75 years) were followed for a median of 6 years. Use of ACE inhibitors (both as a class and by central activity) was compared with other anti-HTN agents to assess whether they were associated with a lower risk of incident dementia, cognitive decline (by Modified Mini-Mental State Examination [3MSE]), or incident disability in instrumental activities of daily living (IADLs).

**Results:** There were 158 cases of incident dementia among 414 participants who were exposed to ACE inhibitors and 640 who were not. When compared with anti-HTN drugs, there was no association between exposure to all ACE inhibitors and risk of dementia, difference in 3MSE scores, or odds of disability in IADLs, and adjusted results were similar. However, ACE inhibitors that had central activity were associated with 65% less decline in 3MSE scores per year of exposure ($P = 0.01$), and non-centrally active ACE inhibitors were associated with a greater risk of incident dementia and greater odds of disability in IADLs compared with other anti-HTN drugs.

**Conclusions:** ACE inhibitors, as a class, may not be associated with dementia risk or cognitive decline in older hypertensive adults. However, there may be significant within-class differences in regard to these outcomes.

**Reviewer's Comments:** The prevalence of dementia in the United States is projected to increase to approximately 10 million by 2050. Therefore, medication that can delay onset of dementia will have a significant impact on health care. Biologically, ACE inhibitors may benefit cognition by anti-inflammatory actions and blocking of ACE activity in the cerebral cortex, which is increased in patients with dementia. Randomized clinical trials should be conducted to investigate the effects of a centrally acting ACE inhibitor in preventing dementia and cognitive decline. (Reviewer-Suraj Maraj, MD).

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Keywords: Cognitive Decline, Elderly, Hypertension

Print Tag: Refer to original journal article
Use CTA to Complement Coronary Angiography in CABG Patients

Diagnostic Accuracy of Computed Tomography Angiography in Patients After Bypass Grafting.

Weustink AC, Nieman K, et al:

JACC Cardiovasc Imaging 2009; 2 (July): 816-824

Background: Coronary CT angiography (CTA) has shown promise in the noninvasive evaluation of coronary arteries.

Objective: To assess the accuracy of dual-source 64-slice CTA in the evaluation of patients after CABG.

Participants/Methods: 52 consecutive symptomatic patients (mean age, 66.6 ± 13.2 years; 41 male) underwent CTA before invasive coronary angiography, and the findings were compared.

Results: 102 venous graft segments were evaluated, and CTA correctly identified 15 of 15 occluded segments and 13 of 13 significant stenoses (>50% luminal narrowing). Of 50 arterial segments evaluated, CTA correctly identified 1 of 1 occluded left internal mammary artery graft. CTA identified 19 of 20 significant stenoses in 142 distal runoff segments. Of 289 native grafted coronary artery segments, CTA identified 170 significant stenoses, but 5 lesions were overestimated. Of 118 non-grafted coronary artery segments, CTA detected 33 significant stenoses; however, 7 were overestimated and 1 lesion was missed. Lack of tube current modulation led to a fairly high radiation dose of 22.1 mSv compared with 8.8 mSv for invasive angiography.

Conclusions: Dual-source 64-slice CTA was highly accurate in identifying stenosis in bypass grafts, but was less accurate in identifying disease in the native coronary arteries and distal runoff vessels.

Reviewer's Comments: This study shows 100% sensitivity and specificity in identifying significant stenosis in venous and arterial grafts. The sensitivity and specificity for detecting significant stenosis in distal runoffs were 95% and 100%; in all grafted segments, 100% and 96%; and in all non-grafted segments, 97% and 92%, respectively. The sensitivity and specificity is higher than that reported from studies using single-source 64-slice CTA, despite including all segments regardless of image quality for analysis. While detection of stenosis in grafts, which are large caliber vessels, was excellent, CTA tended to overestimate lesion severity in native vessels and missed 2 obstructive lesions. In symptomatic post-CABG patients, where accurate diagnosis of the lesion is essential, invasive coronary angiography would still be required. Of note, the American College of Cardiology Foundation Appropriateness Criteria lists routine use of 64-slice CT coronary angiography in post-CABG patients as an inappropriate/uncertain indication. However, CTA may have a role in reliably assessing graft patency only and may provide complementary anatomic information that may be useful during subsequent coronary intervention. (Reviewer-Anoop C. Parameswaran, MD).

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Keywords: Dual-Source, CT, CABG

Print Tag: Refer to original journal article
Capillary Recruitment Impaired in Patients With DM, MC

Abnormal Skeletal Muscle Capillary Recruitment During Exercise in Patients With Type 2 Diabetes Mellitus and Microvascular Complications.

Womack L, Peters D, et al:

J Am Coll Cardiol 2009; 53 (June 9): 2175-2183

Capillary recruitment during low- and high-intensity exercise is normal in uncomplicated type 2 diabetes mellitus, but it is impaired in those with microvascular complications.

**Background:** Evidence suggests that abnormal skeletal muscle capillary responses in insulin-resistant patients contribute to impaired glucose metabolism and probably to microvascular complications in type 2 diabetes mellitus (DM). In normal patients, a carbohydrate-rich meal stimulates a rapid expansion of skeletal muscle capillary blood volume (CBV) due to hyperinsulinemia mediated by nitric oxide (NO). Glucose uptake is augmented by the increase in the permeability-surface area, giving more access of glucose and insulin to the muscle interstitium. CBV does not increase normally in response to insulin in insulin-resistant patients. Patients with type 2 DM have lower total oxygen consumption and total body glucose uptake during submaximal exercise, which may be due to impaired microvascular flow responses.

**Objective:** To use contrast ultrasound perfusion imaging to determine whether augmentation in CBV or capillary blood flow in skeletal muscles is impaired during low- or high-intensity exercise in patients with DM, and whether responses are more severe in patients with microvascular complications (MC) and DM. The contribution of blood rheology to flow impairment was also evaluated.

**Participants/Methods:** 20 adult healthy patients and 30 obese patients with type 2 DM were compared. Eight DM patients had MC, defined as proteinuria or neuropathy. Brachial artery blood flow and forearm skeletal muscle perfusion were measured using contrast-enhanced ultrasound (CEU). Measurements were taken at baseline and at low- and high-intensity handgrip exercise. Two rheological factors that influence vascular resistance at the capillary level were measured: erythrocyte deformability and whole blood viscosity.

**Results:** Erythrocyte deformability was similar between cohorts, but mean blood viscosity was increased significantly in DM plus MC patients. In healthy patients and in DM patients without MC, skeletal muscle blood flow increased in both low- and high-intensity exercise, largely because of an increase in CBV consistent with microvascular recruitment. In DM with MC patients, blood flow in response to exercise did not increase as much due to blunted CBV response, suggesting impairment in exercise-mediated capillary recruitment. This study showed that skeletal muscle capillary responses to handgrip exercise are preserved in patients with well-controlled uncomplicated type 2 DM, but are impaired in those with MC. Changes in CBV were abnormal in DM with MC despite similar brachial blood flow in the study groups.

**Conclusions:** Capillary recruitment is impaired in patients with DM and MC at low- and high-intensity handgrip exercise. Rheological abnormalities associated with insulin resistance may play a role.

**Reviewer’s Comments:** Abnormal capillary recruitment as a response to exercise is seen in patients with DM and MC. This could contribute to abnormal glucose homeostasis. The technique used in this study to measure capillary recruitment may be useful to evaluate interventions such as drugs or exercise in this patient population. (Reviewer-Marjorie Stanek, MD).

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Keywords: Capillary Recruitment, Diabetes, Microvascular Complications, Exercise

Print Tag: Refer to original journal article
Non-ionic, low-osmolar contrast agents may be as safe as iso-osmolar contrast in preventing renal failure.

**Background:** Contrast-induced acute kidney injury (CI-AKI), particularly after coronary angiography, has been associated with longer hospital stays and greater long-term morbidity and mortality. As such, IV contrast agents have evolved to reduce the risk of CI-AKI. Based on studies demonstrating the superiority of iodixanol (iso-osmolar contrast) over some low-osmolar contrast media (LOCM) in the prevention of CI-AKI, the American College of Cardiology recommends use of iodixanol in patients with chronic kidney disease.

**Objective:** To perform a meta-analysis of all relevant trials comparing iodixanol to LOCM in order to determine whether this recommendation is justified.

**Methods:** Studies published between 1980 through November 2008 were included if they randomized patients to iodixanol versus LOCM and if renal function was routinely assessed on all patients. The primary end point was development of CI-AKI as defined by the study protocol.

**Results:** Of 120 articles reviewed, 16 satisfied the criteria of comparing iodixanol to LOCM in a randomized study with routine assessment of renal function. Of 2763 patients, 1383 were randomized to iodixanol and 1380 to LOCM. All 16 trials used change in creatinine as a primary or secondary outcome, and 9 involved coronary angiography. The remaining studies involved IV contrast exposure. There were no significant differences in baseline characteristics between groups in each of the studies. Twelve of 16 trials studied patients with an elevated mean baseline creatinine. Though there was a trend toward lower risk with iodixanol, overall, there was no significant difference in risk of CI-AKI between iodixanol and LOCM. Also, no difference was seen in the subgroups involving coronary angiography or patients with diabetes. A stratified analysis revealed that iodixanol was, in fact, safer than ioxaglate or iohexol, but it was similar in safety to iopamidol, iomeprol, ioversol, and iopromide. There were no differences overall between groups in need for hemodialysis or in mortality. Interestingly, hemodialysis was exceedingly rare, occurring in 2 patients in the iodixanol group and 9 in the LOCM group.

**Reviewer’s Comments:** Conclusions/Reviewer’s Comments: The major finding in this study contradicts the results of a prior meta-analysis in that iso-osmolar contrast (iodixanol) was not found to be safer in terms of preventing CI-AKI than LOCM. There were, however, some differences in the relative safety among LOCM. The ionic agent, ioxaglate, and the more viscous iohexol were both found to be less safe compared with iodixanol, and should probably be avoided, although the mechanisms for CI-AKI are still not perfectly clear. The authors suggest that, given the lack of significant difference in safety, cost may also need to be factored in to the decision behind choice of contrast agent. (Reviewer-Parul B. Patel, MD).