n-3 Polyunsaturated fatty acids improve ejection fraction, diastolic function, and functional capacity in nonischemic cardiomyopathy patients with mild and moderate heart failure.

**Background:** There is evidence that n-3 polyunsaturated fatty acids (PUFAs) reduce mortality and hospitalizations for cardiovascular reasons in patients with New York Heart Association (NYHA) functional class II to IV regardless of etiology and left ventricular ejection fraction (LVEF).

**Objective:** To test the hypothesis that n-3 PUFAs improve LVEF in stable nonischemic dilated cardiomyopathy. In addition, the effects of n-3 PUFAs on left ventricular diastolic function, functional capacity (peak oxygen uptake [VO\textsubscript{2}]), and NYHA class was studied.

**Methods:** P with ejection fraction ≤45% with no or minimal symptoms on evidence-based medical therapy were included. Patients were randomized to 2 g of n-3 PUFAs or placebo. The primary end point was the change in LVEF between baseline and 12-month follow-up. Secondary end points included a change in left ventricular diastolic function, change in peak VO\textsubscript{2}, and change in NYHA class at 12-month follow-up.

**Results:** 133 patients participated in the study, with 66 in the placebo arm and 67 in the treatment group. In patients randomized to n-3 PUFAs, a significant increase in ejection fraction was noted at 12-month follow-up (10.4% ± 9.5%; \( P < 0.001 \)). Patients randomized to placebo had a significant decrease in ejection fraction during the same period (−5.0 ± 3.8%; \( P < 0.001 \)). There were also significant improvements in measures of diastolic function. Patients treated with n-3 PUFAs had significant increases in peak VO\textsubscript{2} and exercise time, while those randomized to placebo had a significant decrease in peak VO\textsubscript{2} and exercise time. In the placebo group, 71.2% remained in the same NYHA class while 28.8% increased their NYHA class, suggesting clinical worsening. In the treatment group, 73.1% maintained their initial NYHA class, while 26.9% had a lower functional class, suggesting clinical improvement. Although not a prespecified end point, there were also a significantly lower number of hospitalizations for cardiovascular causes and/or worsening heart failure in the treatment group.

**Conclusions:** In this randomized controlled trial of stable patients with nonischemic dilated cardiomyopathy, n-3 PUFA use at 1 year improved systolic and diastolic function as well as functional capacity. This study is limited by small sample size and results that cannot be generalized to heart failure patients with different etiologies or those with more advanced disease.

**Reviewer’s Comments:** Impressive beneficial effects of n-3 PUFAs were noted in this study in earlier stages of nonischemic dilated cardiomyopathy. This study, along with other data, suggests the possibility that n-3 PUFAs are most effective when given early in the disease course. Although the results cannot be generalized to all heart failure patients, the study should renew discussion and research on what exactly the role for n-3 PUFAs should be in the heterogeneous heart failure population. (Reviewer-Stephen Olex, MD).

Keywords: N-3 Polyunsaturated Fatty Acid, Nonischemic Cardiomyopathy

Print Tag: Refer to original journal article
Apixaban lowers stroke rates in atrial fibrillation patients compared to aspirin.

**Background:** Warfarin decreases stroke in patients with atrial fibrillation (AF), but significant variation in effectiveness and dosing increases the potential for adverse events, thus limiting its use. Aspirin leads to some stroke reduction in patients who do not tolerate or do not wish to be placed on warfarin. This therapy is slightly improved by the addition of clopidogrel but with an increased risk of hemorrhage. Apixaban is a factor Xa inhibitor that may be a suitable substitute.

**Objective:** To determine the safety and efficacy of apixaban versus aspirin in stroke reduction in patients with AF in whom warfarin was unsuitable.

**Design/Methods:** This prospective, multicenter trial randomized patients with AF having at least 1 risk factor for stroke (history of stroke/TIA, age ≥75 years, hypertension, diabetes, heart failure, low ejection fraction [≤35%] or peripheral vascular disease), who could not take warfarin because of previous or expected unsuitability, to receive apixaban 5 mg twice daily or aspirin at 81 or 324 mg/day.

**Results:** Over 5500 patients were enrolled. Warfarin had previously been used in 40% of patients but discontinued because of inability to maintain the target international normalized ratio, previous adverse event not related to bleeding, previous serious bleeding, issues or concerns about compliance with blood draws, patient desire, or because the stroke risk was deemed not to be high enough. The study was terminated early because of significant results. The risk of ischemic or hemorrhagic stroke was 1.6% in the apixaban group and 3.7% in the aspirin group ($P < 0.001$). The death rate was lower in the apixaban group (3.5% vs 4.4%; $P = 0.07$) as was the rate of hospitalization for cardiac causes (12.6% vs 15.9%; $P < 0.001$). Bleeding rates were not significantly different between the two groups.

**Conclusions:** Compared to aspirin, apixaban reduces the risk of stroke without increasing the risk of bleeding in patients with AF who are unable or unwilling to take warfarin.

**Reviewer’s Comments:** This study builds on the promising results of the Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) trial, which studied dabigatran as a replacement to warfarin for stroke reduction in AF patients. It appears that the future of stroke reduction for AF will be focused around 1 of these increasing number of nonwarfarin agents on the horizon. While these results are exciting, they must be viewed with caution as the study drug was compared to aspirin and not warfarin or dabigatran. Interestingly, apixaban proved to lower stroke rates in patients with CHADS$_2$ scores of 0 or 1 over aspirin, suggesting a possible change to AF management guidelines in the future. (Reviewer-Sumeet K. Mainigi, MD).

**Keywords:** Apixaban, Stroke, Atrial Fibrillation

**Print Tag:** Refer to original journal article
Automatic referral to cardiac rehabilitation (CR) coupled with a discussion with a healthcare provider about CR increases enrollment in such programs by 45% as compared to such referrals left to the discretion of the treating physician alone.

**Background:** Cardiac rehabilitation (CR) participation has been shown to reduce morbidity and mortality to a similar degree as statins, aspirin, and beta-blockers and is recommended as the standard of care in clinical practice guidelines for acute coronary syndromes and revascularization. One principal barrier to CR utilization is referral failure. No studies have prospectively and concurrently compared various strategies to improve CR referrals.

**Objective:** To compare 4 CR referral strategies (automatic [embedded in discharge orders], liaison [discussion with healthcare provider or peer], combined automatic and liaison; and usual [leaving it up to the physician]) to determine their effects on CR referral and utilization.

**Design:** Prospective controlled study.

**Participants:** 1809 patients with coronary artery disease who were candidates for CR.

**Methods:** All patients were assigned to 1 of the 4 referral groups, and at 1-year follow-up, they completed a survey that assessed CR utilization. Referral strategies were compared.

**Results:** There was greater CR referral for all referral strategies when compared with usual referrals ($P<0.001$). Referral strategy was significantly related to referral and enrollment ($P<0.001$), but not to the degree of participation ($P=0.88$). Combined automatic and liaison referral was the most effective (OR, 8.41; 85.8% referral, 73.5% enrollment), followed by automatic (OR, 3.27; 70.2% referral, 60.0% enrollment), and liaison (OR, 3.35; 59% referral, 50.6% enrollment) as compared with usual referral (32.2% referral, 29.0% enrollment).

**Conclusions:** Combined automatic and liaison referrals for CR achieve the highest referral and enrollment patterns for CR.

**Reviewer's Comments:** Regardless of its recognized benefits, CR remains exceedingly underutilized, primarily due to low rates of referral. This study is the first prospective multicenter comparison of CR referral, enrollment, and participation rates following 4 different inpatient referral strategies. When compared with the usual CR referral left to the discretion of the treating physician, the combined automatic and liaison referral resulted in an 8-fold increase in the likelihood of referral to CR and a 45% boost in enrollment in CR. Regardless of referral strategy, once referred, CR participation rates were consistently >80% of prescribed sessions. These results suggest that broader implementation of combined automatic and liaison-based referral strategies should be encouraged. (Reviewer-Debra L. Braverman, MD).

**Keywords:** Cardiac Rehabilitation, Referral Practices
Utilization of inflammatory markers could be helpful in the management of acute pericarditis.

**Background:** Acute pericarditis is an inflammatory disease, and markers of inflammation could be useful in establishing the diagnosis, disease activity, and length of treatment; However, the role of such markers is not well defined.

**Objective:** To assess the changes in plasma high-sensitivity C-reactive protein (hs-CRP) levels in acute pericarditis and to define the relationship between this level and diagnosis, therapy, and prognosis of acute pericarditis.

**Design/Methods:** The study is a prospective cohort study of all consecutive cases of acute pericarditis within 24 hours from symptom onset. Hs-CRP levels were collected at presentation and then every week until normalization. Empirical anti-inflammatory therapy with aspirin, ibuprofen, or indomethacin was prescribed to all patients for 7 days, and then tapered for 3 to 4 weeks; colchicine or prednisone was added according to the treating physician's discretion.

**Results:** Out of 240 consecutive patients diagnosed with acute pericarditis, 200 patients with viral and idiopathic etiologies were included in the study. At presentation hs-CRP was normal in 44 cases (22%), but only in 7 patients (3.5%) were the hs-CRP levels persistently normal. At week 1, 120 patients (60%) had normal hs-CRP levels, 170 (85%) had normal levels at week 2, 190 (95%) at week 3, and all patients (100%) at week 4. During the 24 months of follow-up, 66 patients (33%) had persistence of symptoms or incomplete response to anti-inflammatory therapy at 1 week, 70 patients (35%) had a recurrence of acute pericarditis, and 4 patients (2%) had cardiac tamponade.

**Conclusions:** Hs-CRP was elevated in 78% of patients with acute pericarditis, persistent elevated levels identified patients at higher risk for recurrence, and normalization of levels indicated resolution of disease activity.

**Reviewer's Comments:** It is universally accepted that inflammation is the major pathologic process in acute pericarditis, and still, the role of anti-inflammatory markers in its diagnosis and time course of disease is unknown. There is still no biologic marker for diagnosis of acute pericarditis, the appropriate length of therapy is unknown, and drugs are administered empirically. Imazio et al (the authors of this study) followed the levels of hs-CRP in patients with acute pericarditis and found evidence that hs-CRP levels are helpful in establishing the diagnosis, in predicting recurrences, in monitoring disease activity, and in determining the length of anti-inflammatory drug therapy. This study is encouraging, and if more comprehensive studies will support these findings, assessing baseline and weekly hs-CRP levels could soon become routine practice in managing patients with acute pericarditis. (Reviewer—Raul Moldovan, MD).

**Keywords:** Acute Pericarditis, CRP, Diagnosis, Therapy, Prognosis

**Print Tag:** Refer to original journal article
Doubling Clopidogrel Dose Post-PCI Does Not Affect Risk of Ischemic Events

Standard- vs High-Dose Clopidogrel Based on Platelet Function Testing After Percutaneous Coronary Intervention: The GRAVITAS Randomized Trial.

Price MJ, Berger PB, et al:

JAMA 2011; 305 (March 16): 1097-1105

Doubling the dose of clopidogrel among post-percutaneous coronary intervention patients with high on-treatment platelet reactivity does not improve ischemic outcomes.

**Background:** High platelet reactivity while on dual antiplatelet therapy with aspirin and clopidogrel has been associated with a higher risk of ischemic events post-percutaneous coronary intervention (PCI). An optimal treatment strategy for patients with high platelet reactivity has not been defined.

**Objective:** To compare the efficacy of standard-dose clopidogrel therapy to high-dose clopidogrel therapy among patients post-PCI with high platelet reactivity.

**Design/Participants:** Multicenter trial that included patients who underwent PCI with a drug-eluting stent and were treated with clopidogrel and aspirin according to standard guidelines.

**Methods:** Patients subsequently underwent testing with a validated point-of-care platelet function test, the VerifyNow P2Y12 test, 12 to 24 hours post-PCI. Patients with high on-treatment platelet reactivity were randomized to either continue standard-dose clopidogrel (75 mg daily) or to high-dose clopidogrel (600 mg on day 1, followed by 150 mg daily) for the next 6 months. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or stent thrombosis. The key safety end point was severe or moderate bleeding.

**Results:** Between July 2008 and April 2010, a total of 5,429 North American patients were screened, and 2,214 (40.8%) were identified as having high on-treatment platelet reactivity. These patients were randomized to either standard- or high-dose clopidogrel therapy. At 6 months, there was no difference in the incidence of the primary end point (standard dose: 25 (2.3%), high-dose: 25 (2.3%); \( P = 0.97 \)). In comparison, of the nonrandomized patients that had an adequate response to clopidogrel at baseline, 8 (1.4%) met the primary end point (in comparison to randomized patients; \( P = 0.20 \)). The rate of moderate or severe bleeding leading to drug discontinuation was similar in all groups regardless of on-treatment reactivity or clopidogrel dose and was \( \leq 1\% \) in each group.

**Conclusions:** Doubling the clopidogrel dose among patients with high on-treatment platelet reactivity after PCI did not affect the risk of ischemic events within the first 6 months.

**Reviewer’s Comments:** This important study demonstrated that doubling the dose of clopidogrel among patients found to have high on-treatment platelet reactivity 12 to 24 hours after PCI was of no benefit in terms of reducing cardiovascular events. However, patients were also serially tested for platelet reactivity up to 6 months post-PCI, and the results indicated that on-treatment platelet reactivity was not stable over time. In up to 38% of patients with high on-treatment platelet reactivity at baseline and then randomized to standard-dose clopidogrel, subsequent testing indicated an adequate platelet response at follow-up. Future studies are needed to identify the optimal timing of testing and to study other available treatments for high on-treatment platelet reactivity such as prasugrel, a third-generation thienopyridine. (Reviewer-Parul B. Patel, MD).

Keywords: Percutaneous Coronary Intervention, Clopidogrel, Platelet Function Testing

Print Tag: Refer to original journal article
Lesion-Related Risk Factors for Atherosclerotic Plaques That Lead to ACS

A Prospective Natural-History Study of Coronary Atherosclerosis.

Stone GW, Maehara A, et al:


In acute coronary syndrome patients who undergo percutaneous intervention, major adverse cardiovascular events occurring during follow-up are equally attributable to recurrence at the site of culprit lesions and to non-culprit lesions.

**Background:** Although we know that atherosclerotic plaques that lead to acute coronary syndrome (ACS) occur at sites of mild stenosis, lesion-related risk factors are not understood well.

**Design/Participants:** Prospective study of 697 patients (median follow-up, 3.4 years) with ACS who underwent 3-vessel coronary angiography and gray-scale and radiofrequency intravascular ultrasonographic (IVUS) imaging following percutaneous intervention (PCI). Subsequent major adverse cardiovascular events (MACEs) were adjudicated to be related to either culprit or non-culprit vessels.

**Methods:** Patients with ACS were enrolled after successful PCI for all lesions believed to be responsible for the index event. Angiography was followed by both gray-scale and radiofrequency IVUS of the left main coronary artery and major proximal epicardial arteries. Clinical follow-up occurred at 30 days, 6 months, and then yearly. On the basis of follow-up angiography, MACEs were adjudicated to have occurred at culprit or non-culprit lesions.

**Results:** The strongest patient level predictor of non-culprit lesion-related MACE was insulin-requiring diabetes mellitus. Time to event (3-year cumulative MACE) was estimated by the Kaplan-Meier method. At 3 years, the rate of recurrent MACE was 20.4%. The culprit lesion related rate was 12.9%, and the non-culprit lesion related rate was 11.6%.

**Conclusions:** In this study, coronary angiography and gray-scale and radiofrequency IVUS were useful to assess coronary arteries in patients who had undergone successful PCI for ACS. Independent correlates of MACE related to non-culprit lesions were insulin-requiring diabetes mellitus, previous PCI (patient characteristics) and plaque burden 70%, thin-cap fibroatheroma (TCFA), and minimal luminal area ≤4 mm2 (lesion characteristics). MACE during follow-up was equally attributable to recurrence at the culprit lesion as well as non-culprit lesion site.

**Reviewer's Comments:** This is a well-conducted study pertaining to the natural history of progression of atherosclerosis. The basic premise of the study is that ACS arises from atheromas with certain histopathological features that are not necessarily dependent on the degree of angiographic stenosis at the site. This study is novel in that it used radiofrequency IVUS, which has been shown to correlate somewhat with histological features of the vessel wall. Fifty-one percent of non-culprit lesion-related recurrent events occurred at sites of TCFA. IVUS may thus help identify plaque characteristics that predispose to ACS and thus MACE. Specificity is lacking for this method. Furthermore, only the proximal coronary anatomy is studied, which is a significant drawback. Although IVUS is a promising technique in the evaluation of coronary atherosclerosis, its practical role in this clinical setting is unclear. The authors also mention imaging-related complications in the study group (1.6%). (Reviewer-Anil George, MD).

Keywords: Atherosclerosis, Acute Coronary Syndrome, Culprit Lesion

Print Tag: Refer to original journal article
In patients revascularized by coronary artery bypass grafting, continued treatment is associated with a lower risk of death or recurrent myocardial infarction.

**Background:** It is unknown whether patients who have undergone coronary artery bypass grafting (CABG) benefit from clopidogrel. Current recommendations support continued use of clopidogrel for 9 to 12 months for acute coronary syndrome patients revascularized by CABG.

**Design/Participants:** Danish registry-based observational cohort study of 3,545 patients who underwent CABG within 180 days after a first-time MI and survived for >30 days after CABG.

**Methods:** Patients were stratified according to clopidogrel treatment and matched using a propensity-score matched population. This score was based on patient probability of receiving clopidogrel by multivariate regression analysis. Outcome measures were all-cause mortality, combined end point of death from recurrent MI or death from any cause, and recurrent MI.

**Results:** 957 (27%) of the 3,545 patients were included in the clopidogrel group based on the fact that they had claimed a prescription for it within 30 days after CABG. The propensity score-matched population consisted of 945 patients. Higher initiation rates for clopidogrel after CABG were related to year of admission, statin and proton pump inhibitor usage, prior percutaneous intervention, and female sex for patients without pre-CABG clopidogrel and year of admission for patients with pre-CABG clopidogrel. Lower initiation rates were related to the use of vitamin K antagonists, low-income, and time to CABG for patients without pre-CABG clopidogrel. The mean follow-up was 466 ± 144 days. Fourteen patients (1.5%) in the clopidogrel group died (any cause) compared to 136 deaths (5.3%) in the non-clopidogrel group (P <0.0001). The combined end point for recurrent MI or all-cause mortality occurred in 39 patients (4.1%) in the clopidogrel group versus 203 patients (7.8%) in the non-clopidogrel group. Overall cardiovascular mortality was lower in the clopidogrel group. The risk of MI was no different in the 2 groups.

**Conclusions:** The use of clopidogrel in CABG patients who had an MI was 27%. First-time MI patients who underwent CABG and continued clopidogrel had a lower death rate and a lower combined end point of recurrent MI and death. There was no difference in the rates of recurrent MI in either group, and bleeding rates after discharge were comparable in both groups.

**Reviewer's Comments:** Data on continued use of dual antiplatelet therapy in patients who have undergone CABG has been conflicting. The sample size is large, and the authors have tried to improve the strength of the study by using a propensity score to match the study subjects. Due to its observational nature, it is unclear whether the observed benefits in the clopidogrel group can be considered causal. The use of surrogates for diagnosis and medication can be sources of error. The observed lack of difference in the risk of MI may be because those patients suffered a fatal outcome. A randomized clinical trial can answer the question. (Reviewer-Anil George, MD).

**Keywords:** Coronary Artery Bypass Grafting, Clopidogrel, Recurrent MI

**Print Tag:** Refer to original journal article
Patients with implantable loop recorders should have remote monitoring activated to enhance the utility of those devices.

Background: The use of remotely monitored implantable loop recorders (ILR) for the detection of arrhythmias has increased significantly over the past few years. The wealth of data provided by these devices is becoming increasingly useful in the detection and documentation of various arrhythmias and unexplained syncope.

Objective: To assess the utility of remote monitoring of ILRs and patient acceptance of those devices in the evaluation of syncope and palpitations.

Design/Participants: Prospective study of patients >18 years of age who had at least 2 episodes of unexplained palpitations or syncope.

Methods: All patients received the Medtronic Reveal ILR and the remote monitoring system (CareLink®). Patients were instructed to initiate remote transmissions weekly or more frequently if warranted by events. In-office visits were conducted every 3 months. When patients activate the ILR, it records the 6.5 minutes preceding and 1 minute following the activation. Devices also automatically store bradycardic and tachycardic events that meet programmed parameters. The CareLink system uses a wand placed over the device to transmit stored information over the telephone line to a secure Internet website where tracings can be reviewed. A questionnaire was given to each patient to rate their experience with both the ILR device and the CareLink transmission process.

Results: The study enrolled 47 patients (mean age, 64 years; 55% males) with a follow-up period of 20 ± 13 months. The indication for monitoring was syncope or presyncope in 44 patients (94%) and palpitations in 3 patients (6%). There were 1369 total transmissions (median of 26 transmissions per patient). Five patients never had events. The other 42 patients had a total of 247,154 events (2.6% of these events [n=6448] had ECG tracings and the rest were just logs). A total of 976 true relevant events were recorded in 32 individual patients. The rest were false events (ie, artifacts). Asystole represented the most commonly documented true relevant event. There were also 174 symptomatic events (patient activated the ILR to record) that were not found to have a corresponding arrhythmic event. The mean time from implant to detection of a relevant event was 28 days ± 49 days. Considering that the usual time interval between clinic visits is 90 days, the ILR would have saved a mean of 71 days to diagnosis. False arrhythmic events were noted in 81% of patients, mostly asystole and fast ventricular tachycardia. Compliance and acceptance of the ILR was excellent among patients from both physical and mental standpoints.

Conclusions: Remote monitoring of ILR devices enhances their utility, allows for early detection of memory saturation, and is well received by patients.

Reviewer's Comments: Activating the remote monitoring feature for patients with ILR should be the standard of care to avoid diagnostic and treatment delays. (Reviewer-Khalid Almuti, MD).

Keywords: Syncope, Palpitations, Management, Remote Monitoring

Print Tag: Refer to original journal article
Diuretics in Acute Heart Failure -- What You Need to Know

Diuretic Strategies in Patients With Acute Decompensated Heart Failure.
Felker GM, Lee KL, et al:


Administration of loop diuretics in different strategies does not change clinical or safety end points in acute heart failure patients.

**Background:** Despite decades of experience with loop diuretics, there is very little prospective data to guide the use of loop diuretics in acute heart failure.

**Design:** The Diuretic Optimization Strategies Trial study was a prospective, randomized, double-blind trial.

**Participants/Methods:** Patients with acute heart failure of <24 hours, who have been on oral loop diuretic for at least 1 month and had a history of chronic heart failure, were included in this trial. Patients were randomized to low dose (IV dose = total daily oral intake) or high dose (IV dose = 2.5 times their daily oral intake) furosemide and to administration of furosemide by IV bolus or by continuous infusion. The study treatment was continued for 72 hours. At 48 hours, the physician could increase the dose by 50%, maintain current strategy, or switch to open-label oral therapy. After 72 hours, the treatment strategy was left to the discretion of the treating physician. The patients were followed for clinical events to day 60. The primary efficacy end point was patient’s global assessment of symptoms, and the primary safety end point was change in serum creatinine from baseline to 72 hours.

**Results:** 308 patients were enrolled in the study. The mean ejection fraction (EF) was 35%, and 27% of the patients had an EF >50%. On comparing the bolus group versus the continuous infusion group, there were no significant differences in the end point of patient-reported global assessment of symptoms or the change in creatinine in 72 hours. There was no significant difference in the likelihood of switching to oral diuretics at 48 hours. Comparing the low-dose versus high-dose groups, the patients assigned to the high-dose strategy were more likely to change to oral diuretics at 48 hours and less likely to require a 50% increase in the dose at 48 hours. There were no significant differences in the end point of patient-reported global assessment of symptoms or the change in creatinine in 72 hours. In the high-dose strategy group, there was greater net fluid loss, weight loss, and relief from dyspnea. There was no significant difference in the length of stay or composite end point of death, rehospitalization, and emergency department visit within the 60 days of follow-up.

**Conclusions:** In acute heart failure, there were no significant differences in patient-reported global assessment of symptoms or change in renal function when diuretics were administered as high dose versus low dose or IV bolus versus continuous infusion.

**Reviewer's Comments:** In common clinical practice, the choice of dose and method of administration depends on the personal preference of the physician. This study demonstrates that any one of these strategies is equally good. There were no significant differences in the length of stay, clinical, or safety end points. (Reviewer-Pradeep S. Arumugham, MD).

Keywords: Acute Heart Failure, Diuretics

Print Tag: Refer to original journal article
Cross sectional studies can observe an association but do not prove causality; variable A might be the cause of variable B, or the other way around, or both could be related to a third factor.

**Background:** Cross-sectional studies have observed an association between obstructive sleep apnea (OSA) and cardiovascular disease (CVD). It is generally assumed that OSA is a likely contributor to CVD but the converse is also possible; CVD might contribute to progression of OSA. This might be through enhanced CO₂ sensitivity of chemoreceptors and/or stimulation of pulmonary irritant receptors by pulmonary congestion, both of which occur with ventricular dysfunction and might lead to ventilatory instability.

**Participants/Methods:** The Sleep Heart Health Study (SHHS) is a prospective observational study of adults ≥40 of age recruited from several observational studies of CVD in the community, with all subjects having polysomnography (PSG). The 2721 subjects had both baseline and 5-year PSG of sufficient quality for inclusion. Incident myocardial infarction (MI) and heart failure (HF) were recorded along with demographic variables including gender, race, diabetes, body mass index (BMI), and neck circumference.

**Results:** 95 subjects had interval CVD events (between the 2 PSGs) over an average 5.2-year follow-up; 57 had MI and 57 had HF. Mean change in apnea-hypopnea index (AHI) was greater in subjects with incident CVD than without: 5.86 (95% CI, 3.45 to 8.26) versus 2.67 (95% CI, 2.21 to 3.13) (P =0.01). This difference remained statistically significant after multivariable adjustment (P =0.03). Subjects with incident CVD were more likely to have clinically significant progression of AHI (≥5 events/hour) versus those without CVD events (47.4% vs 31.7%; P =0.001). The odds ratio of significant AHI progression in subjects with incident CVD compared to those without was 1.65 (95% CI, 1.07 to 2.92; P =0.02) in the adjusted model. In an effort to determine if worsened sleep-disordered breathing (SDB) was a cause of incident CVD, change in AHI between the 2 PSGs was evaluated with respect to occurrence of CVD events after the second PSG. No difference was found between those with and those without incident events.

**Conclusions:** In an ethnically diverse, community-based sample of middle-aged and older adults, incident CVD was associated with worsening of AHI, even after adjustment for multiple clinical variables. It is unlikely that progression of SDB is simply a marker of increased CVD risk as there was no association between change in AHI and incident CVD after the follow-up.

**Reviewer's Comments:** The SHHS has been central to the study of SDB and CVD. Interestingly, while cross-sectional analysis showed a link between SDB and CVD, the prospective arm of the study showed much weaker associations. The current paper raises the novel possibility that it is CVD that impacts on SDB rather than (solely) the other way around. While much remains to be done to understand the clinical interplay between sleep apnea and CVD, this study expands our thought processes and is likely to lead to important new research. (Reviewer-Gregg S. Pressman, MD, FACC, FASE).
Using current treatments to attain a normal lab value (in this case glycated hemoglobin) in diabetic patients with cardiovascular disease may not reduce risk, and may, in fact, be detrimental.

**Background:** The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial tested a strategy of intensive glucose lowering as a means to reduce cardiovascular events. The trial was terminated early because of increased death rates in the intensive control group versus standard glucose control. The current paper reports 5-year outcomes for the trial.

**Methods:** Participants were 40 to 79 years old, had type II diabetes (for a median of 10 years) with glycated hemoglobin ≥7.5%, and had documented cardiovascular disease or risk factors for same. Subjects were randomized to intensive glucose lowering (glycated hemoglobin <6.0%; 5057 participants) or standard therapy (glycated hemoglobin, 7.0% to 7.9%; 5051 participants). After a mean of 3.7 years, those in the intensive group were transitioned to standard therapy; all subjects were followed until June 2009. The primary outcome was combined stroke, myocardial infarction (MI), and cardiovascular death; the secondary outcome was all-cause mortality.

**Results:** Before the transition, the primary outcome occurred in 2.0% versus 2.2% for intensive versus standard therapy ($P = 0.13$); the difference remained nonsignificant throughout the study. At transition, the rate of MI was lower with intensive therapy (1.08% vs 1.35%; HR, 0.79; $P = 0.01$), while cardiovascular death was nonsignificantly higher; these divergent outcomes remained at study end (1.18% vs 1.42% for MI; $P = 0.01$; 0.74% vs 0.57% for cardiovascular death; $P = 0.02$). At transition, all-cause mortality was higher with intensive therapy (1.42% vs 1.16%; $P = 0.04$), and this difference remained at study termination. In this trial, subjects were also randomized to intensive versus standard blood pressure and lipid-lowering therapy. No interactions between treatment assignments were seen except for a marginally higher mortality in the intensive glucose lowering group also receiving intensive blood pressure lowering.

**Conclusions:** In a population of type II diabetics at high risk of having cardiovascular disease, intensive glucose lowering did not reduce cardiovascular events. In fact, this therapy was associated with higher all-cause mortality. There was no evidence of increased hypoglycemia in the intensively treated group, and we need to search for other causes.

**Reviewer’s Comments:** Though increasing glucose levels are associated with increasing risk of cardiovascular events, it is not necessarily true that adjusting diabetic treatments to achieve normal glycated hemoglobin levels is good for patients. As physicians, we must remember to "first, do no harm." In today's age of evidence-based medicine, this means subjecting all therapies to rigorous clinical trials before accepting them as beneficial. What makes sense does not always turn out to be true; this likely reflects our need to think in new directions and refine our notions of disease and treatment. Specific goals for glycated hemoglobin remain controversial, and it may be the case that intensive glucose lowering is beneficial early in the disease but harmful late in the course of diabetes. (Reviewer-Gregg S. Pressman, MD, FACC, FASE).

**Keywords:** Intensive Glucose Lowering, Cardiovascular Events

**Print Tag:** Refer to original journal article
ST-segment elevation in lead aVR should be looked for during all cardiac exercise testing.

**Background:** ST-segment elevation (STE) in lead aVR in a patient with an acute coronary syndrome (ACS) is an indicator of left main coronary artery (LMCA) or very proximal left anterior descending (LAD) coronary artery occlusion.

**Objective:** To test the hypothesis that STE in lead aVR during an exercise treadmill (ETT) test also indicates LMCA or ostial LAD stenosis. Patients were excluded if they had left bundle branch block, intraventricular conduction delay of ≥120 msec, left ventricular (LV) hypertrophy with strain, >1 mm ST-depression (STD) in multiple lead groups, deep T wave inversions in the anterior precordial leads, or resting STE in aVR.

**Participants/Methods:** Consecutive patients from a hospital database were included in the study if they had (1) significant LMCA or ostial LAD disease (before the first septal perforator), (2) coronary artery disease (CAD) without LMCA or ostial LAD disease; or (3) no significant disease and had undergone an ETT using the standard Bruce protocol in ≤6 months. Not all patients had myocardial perfusion imaging (MPI). Coronary angiograms were analyzed in a blinded fashion. Significant CAD was defined as ≥70% stenosis in the right coronary artery, left circumflex, and mid and distal LAD. Significant LMCA and ostial LAD was present at a luminal diameter ≥50%. Baseline and stress ECG changes were evaluated without knowledge of the cardiac catheterization or perfusion imaging. Only horizontal or up-sloping STE in lead aVR was indicative of ischemia.

**Results:** Significant LMCA or ostial LAD was seen in 75 of 454 patients. No disease was seen in 103. Univariate logistic regression analysis showed that the best ETT predictor of LMCA or ostial LAD stenosis was stress-induced STE in lead aVR. It was the strongest predictor on multivariate analysis. MPI variables predictive of LMCA or ostial LAD lesions in univariate and multivariate analysis are reversible LAD ischemia and post-exercise LV ejection fraction. STE in aVR has a sensitivity of 75% and a specificity of 81%. This test performs best in the intermediate pre-test probability range. Bayesian analysis demonstrated that having ≥1 mm STE in aVR almost tripled the post-test odds of finding significant LMCA or LAD ostial stenosis. aVR is sensitive to proximal anterior and septal ischemia because it monitors the LV cavity.

**Conclusions:** Findings of STE in aVR during ETT have been ignored in the past. This study shows the importance of considering this sign even in the absence of MPI abnormalities.

**Reviewer's Comments:** It makes sense that a sign of high-grade stenosis during an episode of chest pain or ACS would be reasonable to look at during an ETT test. STE in aVR should no longer be ignored. (Reviewer- Marjorie Stanek, MD).

Keywords: ST Elevation, Lead aVR, Left Main CAD, Exercise Treadmill Testing, Imaging

Print Tag: Refer to original journal article
Late (and very late) stent thrombosis can occur years after implant.

**Background:** Late stent thrombosis (LST) after drug-eluting stent (DES) placement usually results from lack of complete endothelialization of stent struts. Atherothrombosis of native arteries is the usual cause of acute coronary syndromes, but there are little data on atherosclerosis and plaque rupture occurring within previously stented coronary segments.

**Methods:** Material from 299 consecutive autopsy cases with stent implantation >30 days (406 lesions) was reviewed; 142 had bare-metal stents (BMS) and 157 had DES (sirolimus or paclitaxel). Deaths were reported as stent-related (thrombosis, restenosis), cardiac but nonstent-related, or noncardiac. Coronary arteries were cut at 2- to 3-mm intervals and histologic sections prepared. Comparisons were made between subjects with BMS and DES.

**Results:** Indications for stent implantation and lesion location were comparable between groups. Stent lengths were significantly longer (22.0 mm vs 16.0 mm; \( P < 0.001 \)), and the use of overlapping stents more common (\( P = 0.005 \)) in DES than BMS. Stent-related death due to thrombosis was more prevalent in DES (20% vs 4%; \( P < 0.001 \)), while in-stent restenosis as a cause of death was more common with BMS (28% vs 7%; \( P < 0.001 \)). Nonstent-related death and noncardiac death were similar between groups. Ruptured plaques and thin-cap atheromas (unstable lesions) were more common in DES versus BMS (\( P = 0.008 \)), whereas intimal thickening (\( P < 0.001 \)) and fibrocalcific plaques (\( P = 0.023 \)) were more frequent in BMS patients. The incidence of any neoatherosclerosis was greater in DES patients than BMS patients (31% vs 16%; \( P < 0.001 \)). Further, atherosclerotic change occurred sooner after implant with DES (420 days [IQR: 361 to 683 days]) vs BMS (2,160 days [IQR: 1,800 to 2,880 days]; \( P < 0.001 \)). The shortest duration for development of a lesion with a necrotic core was 270 days for DES, but 900 days for BMS. The cumulative incidence of neoatherosclerosis was higher in DES versus BMS at all time points examined.

**Conclusions:** While neoatherosclerosis occurs with both types of stents, it is more frequent and occurs earlier in the presence of DES than BMS. Such neoatherosclerosis may be responsible, in part, for LST.

**Reviewer's Comments:** This is a very fascinating study exploring a little known area of stent pathophysiology. While the design of the study precludes statements about the prevalence and overall significance of neoatherosclerosis in the clinical setting, it makes us think in new directions about the very concerning problem of late stent thrombosis. (Reviewer-Gregg S. Pressman, MD, FACC, FASE).

Keywords: Neoatherosclerosis, Drug-Eluting Stents, Bare-Metal Stents

Print Tag: Refer to original journal article
Inpatient cardiac rehabilitation (CR) improves lipid profile, C-reactive protein, blood pressure and obesity indices over 12-months follow-up, and elements of this response are augmented by subsequent outpatient CR.

**Background:** Inpatient phase 2 cardiac rehabilitation (CR) is the standard of care for acute coronary syndrome (ACS) patients in Europe, while such programs in the U.S. are outpatient. The long-term effects of inpatient CR on cardiovascular risk factors are not well documented.

**Objective:** To assess the effects of inpatient CR after ACS treated with primary percutaneous coronary intervention (PCI) and to determine if subsequent outpatient CR leads to supplementary effects.

**Design:** Controlled prospective study.

**Participants:** 54 consecutive CR participants (40 inpatient only [CR_In] and 14 ambulatory CR after inpatient CR was complete [CR_In+Amb]) versus 20 consecutive control patients (No_CR), all 3 weeks after ACS treated with primary PCI.

**Methods:** Inpatient CR included physical training (5 days per week for 3 weeks, moderate intensity exercise expending 1250 to 1500 Kcal) and educational sessions 4 times weekly on cardiovascular risk factor modification, pharmacotherapy, and psychotherapy. At discharge, all patients were offered 3-month outpatient CR that continued the same exercise regimen for 24 sessions. All participants were assessed at baseline, the completion of inpatient CR, at 3 months, and at 12 months with measurements of body mass index (BMI), waist circumference, systolic and diastolic blood pressure (BP), self-reported physical activity, serum fasting glucose (Glc), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), and C-reactive protein (CRP).

**Results:** Baseline data were similar in all groups. BMI increased in all, but the magnitude of change in No_CR was highest. Waist circumference increased only in No_CR. BP at 12 months was lower in both CR groups compared with No_CR, but more so in CR_In+Amb as compared to CR_In. Physical activity in CR_In was higher than No_CR. HDL increased in all groups, most pronounced in CR_In. At 12 months, both CR groups had lower TC, LDL, TG, and CRP than No_CR, while Glc dropped in CR_In+Amb only. All changes were significant.

**Conclusions:** Inpatient phase 2 CR is associated with favorable effects on CRP and blood lipids, and it lessens the increase in obesity indices and blood pressure seen in nonparticipants. Additional ambulatory CR further enhanced blood pressure control.

**Reviewer’s Comments:** The fact that waist circumference did not increase in either CR group suggests that the increase in BMI in the CR patients was not associated with an increase in visceral fat. The lack of improvement in fasting glucose despite increased physical activity in CR patients was likely associated with increase in BMI. Since outpatient CR is underutilized in the U.S. due in large part to low referral and high dropout rates, it may be worthwhile to increase inpatient CR participation options to improve access and participation. (Reviewer-Debra L. Braverman, MD).

Keywords: Cardiac Rehabilitation, Cardiovascular Risk Factors, Exercise Training

Print Tag: Refer to original journal article
Prehypertension, defined as systolic 120 to 139 and/or diastolic 80 to 89, increases the risk of future hypertension and cardiovascular events.

**Background:** Existing trials of antihypertensive therapy to prevent cardiovascular disease (CVD) have produced conflicting results regarding benefit in subjects with normal blood pressure (BP) or prehypertension.

**Design/Objective:** This meta-analysis examined randomized trials of such therapy on secondary prevention of CVD and all-cause mortality among patients without clinical hypertension (hypertension defined as ≥140/≥90, or history of hypertension, or on antihypertensive agents).

**Methods:** Eligible studies were randomized controlled trials of antihypertensive therapy for the prevention of CVD events among patients with pre-existing CVD or CVD equivalent (eg, diabetes). Studies were excluded if they did not include prehypertensive or normal subjects. Outcomes included stroke, myocardial infarction (MI), heart failure (HF), composite CVD, CVD mortality, and all-cause mortality.

**Results:** 25 studies incorporating 64,162 subjects were included. The mean age ranged from 55 to 68 years; the mean study duration ranged from 1.5 to 63 months, and 76% of the subjects were men. Class and dose of antihypertensive medication varied between studies as did history of MI, HF, diabetes, stroke, and coronary disease at baseline. Relative risks were reduced for all outcomes measured: 23% for stroke, 20% for MI, 29% for HF, 15% for composite CVD, 17% for CVD mortality, and 13% for all-cause mortality. There was low heterogeneity between studies for MI and HF events, and moderate heterogeneity for other outcomes. There was no evidence of publication bias, except possibly in the case of stroke.

**Conclusions:** Patients with CVD and BP in the normal or prehypertensive range benefit from antihypertensive therapy. Further work needs to be done evaluating specific subpopulations within the larger group of CVD patients and in diverse racial/ethnic groups.

**Reviewer’s Comments:** How aggressively to treat BP in patients with CVD or at high risk of CVD is an interesting question. To observe that CVD risk increases with increasing BP, even in the normal and prehypertensive ranges, is not the same as saying that applying pharmacotherapy to lower BP reduces risk in those without definite hypertension. Currently, there is no agreement on reducing BP to <140/90 except in diabetics where the goal is <130/80. Even this guideline is based on limited evidence, and the recent ACCORD BP study showed no benefit to lowering systolic <120 compared with <140 in type II diabetics. The current paper suggests treating CVD patients to <140/90 is beneficial in reducing risk of future CVD events. However, before accepting this as a treatment goal, more studies, particularly randomized, controlled, double-blind studies, are needed. In addition, we need data on specific subpopulations, such as diabetics or the elderly. Given that CVD is the leading cause of death in the U.S. and that 70 million adults in this country are prehypertensive, this becomes an issue of paramount importance. (Reviewer-Gregg S. Pressman, MD, FACC, FASE).

**Keywords:** Antihypertensive Therapy, Cardiovascular Disease, Prehypertension

**Print Tag:** Refer to original journal article
New MRI Criteria More Specific but Less Sensitive for ARVD


Vermes E, Strohm O, et al:

J Am Coll Cardiol Img 2011; 4 (March): 282-287

New task force criteria for diagnosing arrhythmogenic right ventricular dysplasia by MRI have high specificity, but may have low sensitivity.

Background/Objective: A recent revision of the original 1994 task force criteria for diagnosis of arrhythmogenic right ventricular dysplasia (ARVD) was proposed. The authors sought to assess the change in prevalence of ARVD by cardiac magnetic resonance imaging (CMRI) using the revised imaging criteria compared to the original recommendation.

Methods: A retrospective analysis of 294 patients referred for CMRI to rule out ARVD was analyzed using both the 1994 criteria and the recently proposed modified imaging criteria. A subset of 134 patients with complete clinical data and tissue characteristics were used to calculate sensitivity and specificity of these criteria.

Results: The mean age of the patients was 43 ± 16 years, and 49% were females. Using the original criteria, 23.5% had major criteria versus 6.5% when using the new criteria; 58.5% had minor criteria using the older task force guidelines versus only 4% when using the new criteria. Ten patients had a definitive diagnosis of ARVD without counting imaging criteria. Using the original criteria, all 10 patients had some CMRI findings (9 met major criteria and 1 had minor criteria). Using the revised criteria, only 4 patients met imaging criteria by CMRI. The specificity for major and minor criteria using the revised criteria was 94% and 96% versus 78% and 39% for the old criteria.

Conclusions: Applying the revised CMRI imaging criteria leads to improved specificity for the diagnosis of ARVD at the expense of decreased sensitivity.

Reviewer's Comments: ARVD is a rare cardiomyopathy usually inherited in an autosomal dominant fashion that can lead to lethal arrhythmias. In most MRI practices, referrals to rule out ARVD are quite common despite the rarity of the disease. A clinical diagnosis is often difficult to establish and requires a combination of clinical, electrocardiographic, tissue findings, and family history. Until recently, imaging the right ventricular free wall by CMRI had been difficult due to technical limitations and false-positive reading being very common. The modification of task force criteria uses more objective criteria such as right ventricular volumes and ejection fraction along with wall motion abnormalities to diagnose possible ARVD. The authors show that these criteria, while very specific may be less sensitive. However, the authors only had 10 confirmed cases of ARVD, while the task force criteria were based on 44 confirmed cases (sensitivity, 68% to 76%; specificity, 90% to 98% for MRI criteria) and are likely more accurate. Moreover, imaging is only one of the several criteria used to diagnose ARVD, and the 6 cases that were “missed” by the modified MRI criteria were picked up by the other clinical and electrocardiographic criteria. (Reviewer-Anoop C. Parameswaran, MD).

Keywords: Cardiomyopathy/Dysplasia, Cardiac Magnetic Resonance, Task Force Criteria

Print Tag: Refer to original journal article
Fractional Flow Reserve Measurement Reliable in Acute MI

Fractional Flow Reserve for the Assessment of Nonculprit Coronary Artery Stenoses in Patients With Acute Myocardial Infarction.

Ntalianis A, Sels J-W, et al:

J Am Coll Cardiol Intv 2010; 3 (December): 1274-1281

Background: Multivessel coronary artery disease is present in as many as half of all patients with acute myocardial infarction (MI). Current guidelines support the acute treatment of the culprit vessel and the noninvasive assessment of nonculprit coronary lesions at a later time, particularly if the patient is otherwise hemodynamically stable. Fractional flow reserve (FFR) measurement is a well-validated invasive method of assessing the hemodynamic significance of coronary stenoses in the catheterization lab. FFR measurement is not recommended to be performed acutely in the infarct-related artery as myocardial microvascular dysfunction might affect the result, making it unreliable. It is not clear whether microvascular dysfunction occurs in the noninfarct territory and whether FFR measurement of nonculprit coronary stenoses might be a reliable means of assessing residual disease.

Objective: To assess the reliability of FFR measurement of nonculprit coronary stenoses in patients with acute MI.

Participants/Methods: Hemodynamically stable patients with ST-segment- or non–ST-segment elevation MI (STEMI or NSTEMI) who underwent percutaneous coronary intervention (PCI) within 72 hours of the onset, and with at least 1 nonculprit coronary stenosis (>50% angiographically) were included. All patients underwent angiography post nitrate administration. PCI of the culprit vessel was performed followed by FFR measurement of the nonculprit stenoses. Four days to 3 months later, catheterization was repeated, with repeat angiography and FFR assessment of the nonculprit stenoses utilizing the pressure guidewire positioned in the same location it had been in previously. The primary end point was the reproducibility of the initial FFR measurement.

Results: 112 patients (75 STEMI and 27 NSTEMI) were initially included, of which 101 underwent repeat measurement. Repeat FFR measurement was performed 35 ± 4 days after initial measurement, with 83% performed >7 days later. Both in STEMI and in NSTEMI, the FFR measurements remained unchanged between the acute and follow-up phases (STEMI, 0.78 vs 0.76; P =ns; NSTEMI, 0.77 vs 0.77; P =ns). The FFR measurements were unchanged even for the angiographically intermediate (40% to 70%) stenoses.

Conclusions: FFR assessment of nonculprit coronary stenoses during acute MI is reliable.

Reviewer’s Comments: FFR measurement of nonculprit coronary stenoses during acute MI is a reliable method of assessing the hemodynamic significance of residual disease. Also, FFR measurement has the added benefit of greater specificity and spatial resolution compared to myocardial perfusion imaging. Of course, in the case of hemodynamic instability or extensive myocardial necrosis, FFR measurement in the acute phase might not be advisable. (Reviewer-Parul B. Patel, MD).

Keywords: Fractional Flow Reserve, PCI, MI

Print Tag: Refer to original journal article
Background: Sudden cardiac death (SCD) among athletes is a dramatic event. Previous studies (Corrado D. 2006) have indicated that prescreening can decrease this tragedy among athletes.

Objective: To investigate the effectiveness of cardiac evaluation and screening among elite athletes in preventing SCD.

Methods: This observational, retrospective study looked at SCD among elite athletes in Israel reported by 2 major newspapers between January 1985 and December of 2009. In 1997, Israel mandated a prescreening of all athletes, including history and physical, resting ECG, and Bruce-protocol exercise testing for all athletes. The authors of this study compared the 12-year incidence of SCD before this law to the 12-year period after this mandate.

Results: There were 24 cases of SCD among elite athletes reported by the 2 major newspapers in Israel during the 24-year period. The average incidence of SCD was calculated at 2.6 events per 100,000 athlete-years. The average yearly incidence of SCD during the decade before the 1997 ECG screening mandate and after the mandate was 2.54 and 2.66 events per 100,000 person-years, respectively ($P=0.88$).

Conclusions: The authors of this study conclude that mandatory screening of competitive athletes does not reduce the risk of SCD.

Reviewer's Comments: The results of this study are surprising and in contrast with the Italian study. As the authors mention, the Italian study compared only 2 years of data before and after the ECG mandate. This study, however, has significant limitations. The authors estimated the number of athletes per year instead of the actual number, which could significantly affect the incidence per year calculation. Also, the authors admit that the very low number of events may have underpowered this study to show a difference. SCD in an athlete is a devastating event, yet a rare one. The investigators are faced with the challenge of finding a screening test that can effectively predict this very unlikely event. It would be interesting to know the autopsy reports (if available) of these athletes to further narrow the actual cause of SCD (ie, hypertrophic cardiomyopathy, anomalous coronaries, arrhythmogenic right ventricular dysplasia, long QT, etc). Perhaps another test modality can more effectively prevent SCD. As of today, we are faced with the choice of the very high cost and associated anxiety of screening tests, which may or may not work, versus the tragedy of an athlete dying on the field. (Reviewer-Behnam Bozorgnia, MD).

Keywords: Sudden Cardiac Death, Competitive Athletes, Mandatory Screening

Print Tag: Refer to original journal article
It may be useful to obtain a preablation MRI to determine the amount of left atrial fibrosis to help guide patient selection and counsel these patients on their chances for procedural success.

**Background:** Atrial fibrillation (AF) is associated with electrical, structural, and contractile abnormalities of the left atrium (LA) that contribute to the maintenance of the arrhythmia. The end result of these progressive abnormalities is fibrosis of parts of the LA. Magnetic resonance imaging (MRI) with delayed enhancement (DE-MRI) is able to quantify the degree of fibrosis in the LA. DE-MRI can also quantify LA scar resulting from radiofrequency ablation (RFA) for the treatment of AF.

**Objective:** To determine if the degree of preablation LA fibrosis predicts success of the RFA procedure.

**Participants/Methods:** This prospective study looked at 144 patients referred for AF ablation. Patients had a pre-procedure DE-MRI to quantify the amount of LA fibrosis as well as a post-procedure DE-MRI 3 months after RFA to determine the amount of ablation-related scarring. Determination of both fibrosis and scarring was based on computerized evaluation. Specific algorithms were used to differentiate ablation-related scarring from preablation fibrosis on post-ablation DE-MRI. Patients were followed clinically every 3 months and wore Holter monitors to document recurrences. Antiarrhythmic drugs were used as needed for early post-ablation AF recurrences (any atrial arrhythmia lasting >30 seconds).

**Results:** Of the 144 MRIs obtained, 120 were of adequate quality for analysis. The average preablation fibrosis was 18% of the LA walls. Patients were classified into 1 of 4 groups based on the amount of fibrosis. Stage I patients had minimal fibrosis (<5%), stage II had mild fibrosis (5% to 20%), stage III had moderate fibrosis (20% to 35%), and stage IV had extensive fibrosis (>35%); there were 7 patients in stage I, 71 in stage II, 23 in stage III, and 16 in stage IV. All 4 groups were similar with regard to age, hypertension, diabetes, coronary artery disease, congestive heart failure, and left ventricular function. The percentage of patients with paroxysmal versus persistent AF was not significantly statistically different between groups (although paroxysmal AF was more prevalent in stage I patients). All 144 patients had adequate images for analysis of post-ablation scarring. Overall scarring 3 months after ablation averaged 15% of the LA wall volume. Scar burden was similar across all groups. It was rare (only 7%) to have all pulmonary veins truly isolated with continuous circumferential scarring on DE-MRI. Following a mean follow-up period of 283 days, 37 patients (31%) had recurrences of atrial arrhythmias. None occurred in stage I patients, 28% in stage II, 34% in stage III, and 56% in stage IV patients. The number of veins encircled was the strongest predictor of recurrence in group II. Age and 3-month scar burden were predictors in group III, while no predictors identified in group IV.

**Conclusions:** Preablation fibrosis and postablation scarring are both useful predictors of clinical AF outcomes.

**Reviewer's Comments:** Preablation fibrosis may help guide the selection of patients for AF ablation. It may better inform patients of their individual chances for success. (Reviewer-Khalid Almuti, MD).

Keywords: Atrial Fibrillation, Catheter Ablation, Atrial Fibrosis