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SCANNING THE LITERATURE

# Summaries of Key Journal Articles

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## Arrhythmias

### Incidence of and Outcomes Associated With Ventricular Tachycardia or Fibrillation in Patients Undergoing Primary Percutaneous Coronary Intervention

**Mehta RH, Starr AZ, Lopes RD, et al., on behalf of the APEX AMI Investigators.**
***JAMA* 2009;301:1779–1789.**

**Study Design:** Does ventricular tachycardia/ventricular fibrillation (VT/VF) affect prognosis in patients undergoing percutaneous coronary intervention (PCI) in the setting of ST-elevation myocardial infarction (STEMI)?

**Methods:** This was a retrospective analysis of a clinical trial in which 5,745 patients (mean age 61 years) presenting with STEMI underwent PCI. Sustained VT/VF was classified as early (i.e., before or during PCI) or late (i.e., after PCI). The 1° outcome was 90-day mortality.

**Results:** VT/VF occurred in 5.7% of patients. The timing of VT/VF was early in 205 patients and late in 117 patients. The VT/VF occurred within 48 hours of STEMI onset in 90% of patients. The 90-day mortality was 3.6% in patients without VT/VF, 17.2% in patients with early VT/VF, and 33.3% in patients with late VT/VF. Early and late VT/VF were associated with a 2.3- and 5.6-fold higher risk of death at 90 days, respectively. Sudden cardiac death accounted for 40% of deaths. The strongest predictors of VT/VF were advanced Killip class, pre-PCI thrombolysis in myocardial infarction (TIMI) flow grade 0, post-PCI TIMI flow < grade 3, and ST-elevation resolution <70%.

**Conclusions:** In patients undergoing PCI for STEMI, VT/VF markedly increases the risk of mortality at 90 days, particularly when the VT/VF occurs after PCI.

**Perspective:** VT/VF in the first 48 hours of STEMI previously was thought to not have long-term prognostic implications. The results of this study and others indicate that VT/VF is a strong independent predictor of death at 90 days. Whether early treatment with an implantable cardioverter defibrillator improves outcomes in these patients is unclear and requires further study.

*Summary written by: Fred Morady, MD*

## General Cardiology

### Cardiorespiratory Fitness as a Quantitative Predictor of All-Cause Mortality and Cardiovascular Events in Healthy Men and Women: A Meta-Analysis

**Kodama S, Saito K, Tanaka S, et al.**
***JAMA* 2009;301:2024–2035.**

**Study Design:** What is the long-term outcome after prophylactic coronary revascularization prior to major vascular surgery in high-risk patients?

**Methods:** This meta-analysis included 33 studies identified after a systemic literature review of observational cohort studies

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published between 1966 and 2008. Eligibility criteria included the assessment of CRF by exercise stress testing with reported maximal aerobic capacity in metabolic equivalent (MET) units. Outcomes of interest included all-cause mortality, and coronary heart disease (CHD) or cardiovascular disease (CVD). Only studies with patients having a disease that was a major risk factor such as diabetes or hypertension, CHD, or chronic heart failure were included.

**Results:** A total of 102,980 participants were included for the analysis of all-cause mortality and 84,323 for the analysis of CHD/CVD mortality. Pooled relative risk of all-cause mortality and CHD/CVD events per 1 MET higher level of maximal aerobic capacity were 0.87 (95% confidence interval [CI], 0.84-0.90) and 0.85 (95% CI, 0.82-0.88), respectively. Subjects with low CRF were at increased risk for all-cause mortality compared to subjects with high CRF (relative risk [RR], 1.70; 95% CI, 1.51-1.92) and CHD/CVD events (RR, 1.56; 95% CI, 1.39-1.75). Subjects with low CRF were also at increased risk for events compared to subjects with intermediate CRF (RR, 1.40; 95% CI, 1.32-1.48 for all-cause mortality and RR, 1.47; 95% CI, 1.35-1.61 for CHD/CVD). Subjects with a maximal aerobic capacity of 7.9 METs or more had significantly lower rates of all-cause mortality and CHD/CVD events.

**Conclusions:** Better CRF was associated with a lower risk for all-cause mortality and CHD and/or CVD events.

**Perspective:** These findings support the need for advising patients to be physically active as a key component of prevention recommendations.

*Summary written by: Elizabeth A. Jackson, MD*

## Effect of Intensive Control of Glucose on Cardiovascular Outcomes and Death in Patients With Diabetes Mellitus: A Meta-Analysis of Randomised Controlled Trials

**Ray KK, Seshasai SR, Wijesuriya W, et al.**
***Lancet* 2009;373:1765–1772.**

**Study Design:** Does intensive control of glucose reduce macrovascular events and all-cause mortality in individuals with type 2 diabetes mellitus?

**Methods:** A meta-analysis was conducted of five prospective randomized controlled trials of 33,040 participants to assess the effect of an intensive glucose-lowering regimen on death and cardiovascular outcomes compared with a standard regimen. Endpoints included information about events of nonfatal myocardial infarction (MI), coronary heart disease (CHD) (fatal and nonfatal MI), stroke, and all-cause mortality.

**Results:** The five trials provided information on 1,497 cases of MIs, 2,318 cases of CHD, 1,127 strokes, and 2,892 cases for all-cause mortality during 163,000 person-years of follow-up (study follow-up ranged from 3.5 to 10.1 years). The mean hemoglobin $A_{1c}$ concentration ($HbA_{1c}$) was 0.9% lower for participants given intensive versus standard treatment. Increased intensity glycemic control resulted in a 17% reduction in events of nonfatal MI (odds ratio, 0.83; 95% confidence interval, 0.75-0.93), and a 15% reduction in CHD events (0.85, 0.77-0.93), but had no significant effect on incident stroke, heart failure, or all-cause mortality. Hypoglycemia occurred in 38.1% of intensive treatment compared to 28.6% of standard treatment.

**Conclusions:** Lowered $HbA_{1c}$ concentration from intensive glycemic control significantly reduces coronary events without an increased risk of death.

**Perspective:** The benefit of tighter glycemic control appears worth the risk, but the impact of increased hypoglycemia is not clear from this analysis. The authors point out that the mean (weighted) mortality rate of participants on standard treatment is 18.6 per 1,000 person-years of follow-up, and those who achieve a 0.9% reduction from a mean $HbA_{1c}$ concentration of 7.8% at baseline have about two less MIs and three fewer CHD events for every 200 individuals treated for 5 years. This benefit is modest compared to the benefit of lipid and blood pressure therapies in diabetes and supports aggressive treatment of all cardiovascular risk factors, including stricter glycemic control, which is also associated with a decrease in microvascular complications.

*Summary written by: Melvyn Rubenfire, MD*

## Health Care-Associated Native Valve Endocarditis: Importance of Non-Nosocomial Acquisition

**Benito N, Miró JM, de Lazzari E, et al., on behalf of the ICE-PCS (International Collaboration on Endocarditis Prospective Cohort Study) Investigators.**
***Ann Intern Med* 2009;150:586–594.**

**Study Question:** What are the characteristics and outcomes of community-associated, and nosocomial and non-nosocomial health care-associated native valve infective endocarditis (IE)?

**Methods:** A prospective study was conducted from June 2000 to August 2005 at 61 hospitals in 28 countries, in patients with definite native valve IE and no history of intravenous drug use. Clinical and echocardiographic findings, microbiology, complications, and mortality were recorded. IE was classified as community-acquired if it was diagnosed within 48 hours of admission in a patient without extensive out-of-hospital contact with health care. IE was considered nosocomial health care-associated if it occurred in a patient hospitalized for more than 48 hours before the onset of signs or symptoms, and non-nosocomial health care-associated if it

was diagnosed within 48 hours of admission in a patient with extensive out-of-hospital contact with health care.

**Results:** Health care-associated native valve endocarditis was present in 557 (34%) of 1,622 patients, including 303 (54%) with nosocomial infection and 254 (46%) with non-nosocomial infection. *Staphylococcus aureus* was the most common cause of health care-associated infection (nosocomial, 47%; non-nosocomial, 42%; p = 0.30); a high proportion of patients had methicillin-resistant *S. aureus* (nosocomial, 57%; non-nosocomial, 41%; p = 0.014). Fewer patients with health care-associated IE had cardiac surgery (41% vs. 51% of community-associated cases; p < 0.001), but more of the former patients died (25% vs. 13%; p < 0.001). Multivariable analysis confirmed greater mortality associated with health care-associated IE (incidence risk ratio, 1.28 [95% confidence interval, 1.02-1.59]).

**Conclusions:** More than one-third of cases of native valve IE involve contact with health care, and out-of-hospital acquisition of infection is common. Clinicians should recognize that outpatients with extensive out-of-hospital health care contacts who develop endocarditis have clinical characteristics and outcomes similar to those of patients with nosocomial infection.

**Perspective:** It makes sense that patients with frequent exposure to health care interventions and other aspects of the health care system are at risk of infection with organisms similar to hospitalized patients. This study helps define this third group of patients. Perhaps this would be easier with a simple change of labels. Linguistically, there is no reason that the term 'nosocomial' should apply exclusively to diseases acquired within the walls of a hospital; simple contact with health care should be enough.

*Summary written by: David S. Bach, MD*

## Cytochrome P450 Genetic Polymorphisms and the Response to Prasugrel. Relationship to Pharmacokinetic, Pharmacodynamic, and Clinical Outcomes

**Mega JL, Close SL, Wiviott SD, et al.**
***Circulation* 2009;119:2553–60.**

**Study Question:** How does polymorphism of cytochrome P450 (CYP) impact the pharmacodynamics and pharmacokinetics of, and clinical response to prasugrel?

**Methods:** The authors studied the associations between polymorphisms of CYP genes, plasma concentrations of active drug metabolite, and platelet inhibition in response to prasugrel in 238 healthy subjects. They further studied the association between these genetic variants with outcomes in a cohort of 1,466 patients randomized to treatment with prasugrel in the TRITON-TIMI 38 trial.

**Results:** There was no significant change in the pharmacokinetics (active metabolite levels) or the platelet inhibition in response to prasugrel with presence (or absence) of at least one reduced-function allele for any of the CYP genes tested (*CYP2C19*, *CYP2C9*, *CYP2B6*, *CYP3A5*, and *CYP1A2*). Among patients with acute coronary syndromes who were randomized to prasugrel, there was no association between the genotype and the risk of cardiovascular death, myocardial infarction, or stroke. A significant interaction was noticed between the impact of the genotype and the randomization arm with respect to ischemic events.

**Conclusions:** Polymorphism of CYP does not influence the active drug metabolite levels, inhibition of platelet aggregation, or the risk of cardiovascular events in patients treated with prasugrel.

**Perspective:** Among patients treated with clopidogrel, presence of reduced-function *CYP2C19* alleles is associated with an exaggerated hazard of major adverse cardiovascular events. It seems that the clinical effect of prasugrel is relatively independent of the genotype, and this may partially explain the superiority of prasugrel observed in the TRITON-TIMI 38 trial. These data, in combination with the authors' earlier work (Mega JL, et al., *N Engl J Med* 2009;360:354–62), provide a strong rationale for pharmacogenetically guided antiplatelet therapy.

*Summary written by: Hitinder S. Gurm, MD*

## Adverse Cardiovascular Outcomes in Women With Nonobstructive Coronary Artery Disease: A Report From the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project

**Gulati M, Cooper-DeHoff RM, McClure C, et al.**
***Arch Intern Med* 2009;169:843-850.**

**Study Question:** Are women with nonobstructive coronary artery disease (CAD) at increased risk for cardiovascular (CV) events?

**Methods:** Women with suspected ischemia and evidence of obstructive CAD on angiography from the Women's Ischemia Syndrome Evaluation (WISE) study were compared to women from the St James Women Take Heart (WTH) project, a community-based sample of women with no history of heart disease at baseline, followed for 10 years. Nonobstructive disease was defined as all coronary arteries with less than a 50% stenosis. Two groups of WISE subjects were created: one with no evidence of CAD and the other with nonobstructive CAD. Subjects from WISE were matched on age and race with subjects from WTH. Mean follow-up time was 5.2 years. Outcomes of interest included CV events (myocardial infarction, stroke, heart failure requiring hospitalization), and death.

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**Results:** A total of 540 women from the WISE study (58.9% with normal coronary arteries and 41.1% with nonobstructive CAD) were compared to 1,000 women from the WTH study. Rates of obesity, family history of CAD, hypertension, and diabetes were lower among the WTH compared to the WISE women. After adjustment for CV risk factors, the 5-year annualized CV event rates were highest for women with nonobstructive (event rate 16%), followed by women with normal coronary arteries (event rate 7.9%). Women in WTH had the lowest event rate at 2.4%. The CV event rate was highest among women with four or more CV disease (CVD) risk factors: 25.3% for women with nonobstructive CAD, 13.9% for women with normal coronary arteries, and 6.5% for asymptomatic women. Increasing age was significantly related to event rates among women with nonobstructive CAD.

**Conclusions:** Women with symptoms and signs suggestive of ischemia, but without obstructive CAD, are at risk for future CVD events, particularly those with multiple CVD risk factors.

**Perspective:** These findings support the need for risk factor prevention, even when coronary arteries appear nonobstructed or normal by angiography. Whether risk factor modification will prevent events in these women remains unanswered.

*Summary written by: Elizabeth A. Jackson, MD*

## Myocarditis

Cooper LT Jr.
*N Engl J Med* 2009;360:1526–1538.

**Perspective:** The following are 10 points to remember about myocarditis:

1. **Epidemiology:** The true incidence of myocarditis is unknown. The greatest burden of pediatric myocarditis may not be apparent for 6-12 years after diagnosis, when children die or require orthotopic heart transplantation for chronic dilated cardiomyopathy.

2. **Etiology:** Viral and postviral myocarditis remain major causes of acute and chronic dilated cardiomyopathy. Seroepidemiologic data are difficult to discern because of the heterotopic effect of enteroviruses, which may result in an amnestic antibody response to other coxsackievirus B strains. The spectrum of viruses in endomyocardial biopsy samples has shifted from coxsackievirus B to adenovirus in the late 1990s and, in the past 5 years, to parvovirus B19 and other viruses, in the United States and Germany.

3. **Etiology:** In Central and South America, *Trypanosoma cruzi* infection can present as acute myocarditis, sometimes with right bundle branch block or left anterior fascicular block. Myocarditis is the most common cardiac pathological finding at autopsy of HIV patients (~50% of cases).

4. **Etiology:** Anticonvulsants, antibiotics, and antipsychotics, have been associated with hypersensitivity myocarditis. Eosinophilic myocarditis has been associated with the Churg–Strauss syndrome, Loffler's endomyocardial fibrosis, cancer, and parasitic, helminthic, or protozoal infections and with vaccination for several diseases, including smallpox.

5. **Etiology:** Giant-cell myocarditis should be considered in acute dilated cardiomyopathy associated with thymoma, autoimmune disorders, ventricular tachycardia, or high-grade heart block.

6. **Pathophysiology:** In animal models, the progression from acute injury to chronic dilated cardiomyopathy is a three-stage process: 1) Acute injury leads to cardiac damage, 2) exposure of intracellular antigens such as cardiac myosin, and 3) activation of the innate immune system that results in mistaken recognition of endogenous heart antigens as pathogenic entities.

7. **Clinical picture:** Although a viral prodrome is classically associated with myocarditis, reported symptoms are highly variable. Children often have a more fulminant presentation.

8. **Tests:** Troponin I has high specificity (89%), but limited sensitivity (34%) in the diagnosis of myocarditis. The sensitivity of the electrocardiogram for myocarditis is low (47%). Fulminant myocarditis may be distinguished from echocardiography by acute myocarditis by a smaller left ventricular cavity size and increased wall thickness. Endomyocardial biopsy should be done in unexplained, new-onset heart failure of less than 2 weeks' duration in association with a normal size or dilated left ventricle and hemodynamic compromise, for suspected fulminant myocarditis.

9. **Diagnostic procedures:** The Dallas diagnostic pathologic criteria are limited by variability in interpretation, lack of prognostic value, and low sensitivity, whereas criteria based on immunoperoxidase staining have greater sensitivity and may have prognostic value. Preliminary data suggest that noninvasive cardiac MRI is an alternative method for diagnosis without the risks of biopsy. Clinicopathological criteria may distinguish fulminant lymphocytic myocarditis from acute lymphocytic myocarditis and introduce prognostically useful data that are better than pathologic criteria.

10. **Treatment:** The mainstay of treatment for acute myocarditis is supportive therapy for left ventricular dysfunction. Most patients will improve with a standard heart failure regimen. Because most are diagnosed weeks after viral infection, it is unlikely that antiviral therapy would be provided early enough to be of benefit. Interferon beta may be effective in patients with viral persistence in chronic, stable dilated cardiomyopathy. The routine use of intravenous immunoglobulin for acute myocarditis in adults is not recommended. Immunosuppression is not beneficial in the routine therapy of acute lymphocytic myocarditis. Unlike lymphocytic myocarditis, transplant-free survival in patients with giant-cell myocarditis

may be prolonged with a combination of cyclosporine and steroids. Patients recovering from acute myocarditis should refrain from aerobic activity for a period of months after the clinical onset of the disease.

*Summary written by: Ragavendra R. Baliga, MBBS*

# Heart Failure/Transplant

## Influence of Patient Age and Sex on Delivery of Guideline-Recommended Heart Failure Care in the Outpatient Cardiology Practice Setting: Findings From IMPROVE HF

Yancy CW, Fonarow GC, Albert NM, et al.
*Am Heart J* 2009;157:754–762.

**Study Question:** What is the influence of age and gender on delivery of optimal heart failure (HF) therapy?

**Methods:** The study cohort was comprised of 15,381 outpatients with chronic HF and left ventricular ejection fraction ≤35% from the IMPROVE HF registry; 71.1% (n = 8,770) were male. Median age of male patients was 70, and 72 for females. The investigators stratified data and then analyzed the patients as male/female and by age tertiles with generalized estimating equation models constructed for seven care measures.

**Results:** There was no difference between the use of angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, aldosterone inhibitors, and cardiac resynchronization therapy (CRT) between male and female patients, but significant differences by gender were observed for anticoagulant therapy, implantable cardioverter defibrillator/CRT-D therapy, and HF education, with higher rates evident for men ($p < 0.001$ for all comparisons). Older patients, particularly older women, were significantly less likely to receive guideline-indicated HF therapies.

**Conclusions:** Patient age and gender were independently associated with reduced rates of some, but not all, HF therapies in outpatient cardiology practices. Older women are especially at risk.

**Perspective:** As the population ages, it is increasingly clear that women have longer life spans than men. The findings of this study that elderly women are receiving less optimal treatment when compared to men is of concern. Bridging the gap between evidence and practice should continue to be the goal of the practicing clinician to improve HF care in the elderly, particularly in women with HF (*Heart Fail Clin* 2007;3:xi-xii).

*Summary written by: Ragavendra R. Baliga, MBBS*

# Interventional Cardiology

## Long-Term Safety and Efficacy of Drug-Eluting Versus Bare-Metal Stents in Sweden

James SK, Stenestrand U, Lindback J, et al., on behalf of the SCAAR Study Group.
*N Engl J Med* 2009;360:1933–1945.

**Study Question:** What is the long-term safety and efficacy of drug-eluting stents (DES)?

**Methods:** The authors evaluated 47,967 patients in Sweden who received a coronary stent and were entered into the Swedish Coronary Angiography and Angioplasty Registry between 2003 and 2006 and for whom complete follow-up data were available for 1-5 years (mean 2.7). In the primary analysis, the investigators compared patients who received one DES (10,294 patients) with those who received one bare-metal stent (BMS) (18,659).

**Results:** Analysis of outcome was based on 2,380 deaths and 3,198 myocardial infarctions (MIs). There was no overall difference between the group that received DES versus BMS in the combined endpoint of death or MI or the individual endpoints of death and MI, and no significant difference in outcome among subgroups stratified according to the indication for stent implantation. Patients who received DES in 2003 had a significantly higher rate of late events than patients who received BMS in the same year, but there was no difference in outcome among patients treated in later years. The average rate of restenosis during the first year was 3.0 events per 100 patient-years with DES versus 4.7 with BMS; 39 patients would need to be treated with DES to prevent one case of restenosis. Among high-risk patients, the adjusted risk of restenosis was 74% lower with DES compared to BMS, and only 10 lesions would need to be treated to prevent one case of restenosis.

**Conclusions:** Compared with BMS, DES are associated with a similar long-term incidence of death or MI, and provide a significant decrease in the rate of restenosis.

**Perspective:** The present study did not demonstrate a difference in long-term survival or in the risk of MI between patients who received DES versus BMS. Among patients who required stents less than 3 mm in diameter and more than 20 mm in length, there was a 70% relative reduction and 10% absolute reduction in clinical restenosis. The data suggest that use of DES is safe, and in patients with lesions at high risk for restenosis, is very effective in reducing the risk of clinical restenosis. DES appears to be the preferred stent in patients at high risk of restenosis provided that the patient is able to afford and tolerate long-term dual antiplatelet therapy.

*Summary written by: Debabrata Mukherjee, MD*

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# Noninvasive Cardiology

## Associations of Dietary Long-Chain n-3 Polyunsaturated Fatty Acids and Fish With Biomarkers of Inflammation and Endothelial Activation (From the Multi-Ethnic Study of Atherosclerosis [MESA])

He K, Liu K, Daviglus ML, et al.
*Am J Cardiol* 2009;103:1238–1243.

**Study Question:** Is dietary intake of n-3 long-chain fatty acids and fish consumption associated with inflammatory biomarkers and markers of endothelial activation?

**Methods:** Data from the Multi-Ethnic Study of Atherosclerosis (MESA) were used for this analysis. The MESA cohort enrolled men and women (ages 45-84 years), with no apparent cardiovascular disease at baseline, between 2000 to 2002. Data on demographic and lifestyle factors were collected, including information on physical activity. Fish and long-chain n-3 polyunsaturated fatty acid consumption was collected with self-administered 127-item food frequency questionnaires for diet over the prior year.

**Results:** A total of 5,677 men and women with no missing dietary information were included. Compared to those in the lowest quartile of polyunsaturated fatty acid consumption, subjects in the highest quartile were more likely to be female, physically active, and have a higher educational level and household income, lower body mass index, and be nonsmokers. Long chain n-3 polyunsaturated fatty acid intake was inversely associated with plasma concentrations of interleukin-6 ($p = 0.01$) and matrix metalloproteinase-3 ($p = 0.03$). Nonfried fish consumption was inversely related to C-reactive protein ($p = 0.045$). Fried fish consumption was inversely related to intercellular adhesion molecule-1 ($p < 0.01$), but not with other biomarkers.

**Conclusions:** Dietary intake of long-chain n-3 polyunsaturated fatty acids and fish was associated with biomarkers, which suggest lower levels of inflammation and endothelial activation, and may explain the cardioprotective effects of fish consumption observed in prior studies.

**Perspective:** These findings from a larger multiethnic observational cohort suggest that consumption of long-chain n-3 fatty acids can be recommended for cardiovascular prevention. Additional information regarding the ratio of n-3 to n-6 fatty acids in this cohort would add to these findings, as some investigators hypothesize that consumption of n-6 fatty acids should be reduced in the typical western diet as a cardiovascular prevention measure.

*Summary written by: Elizabeth A. Jackson, MD*

# Prevention/Vascular

## Association of HTRA1 Mutations and Familial Ischemic Cerebral Small-Vessel Disease

Hara K, Shiga A, Fukutake T, et al.
*N Engl J Med* 2009;360:1729-1739.

**Study Question:** What gene is responsible for cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL)?

**Methods:** Linkage analysis was performed in five families with CARASIL. Sequencing of a candidate gene was performed.

**Results:** CARASIL is linked to a 2.4-Mb region on chromosome 10q, which contains the HTRA1 gene. HTRA1 is a serine protease that represses signaling by transforming growth factor beta (TGF-β) family members. Two HTRA1 missense mutations and one nonsense mutation resulted in protein products that had comparatively low levels of protease activity and did not repress signaling by the TGF-β family members. One nonsense mutation resulted in the loss of HTRA1 protein by nonsense-mediated decay of messenger RNA. Immunohistochemical analysis of the cerebral small arteries in affected persons showed increased expression of the extra domain-A region of fibronectin and versican in the thickened tunica intima and of TGF-β1 in the tunica media.

**Conclusions:** CARASIL is associated with mutations in the HTRA1 gene. Findings indicated a link between repressed inhibition of signaling by the TGF-β family and ischemic cerebral small-vessel disease, alopecia, and spondylosis.

**Perspective:** The genetic cause for this autosomal recessive disorder is unclear. By studying cases from consanguineous families, the authors were able to map and then sequence a candidate gene, which appears to be causally related to this disease. Defects in this gene are associated with a reduced capacity to repress signaling by TGF-β family members. These findings have important therapeutic implications, as agents targeting TGF-β signaling may reduce complications of this disease.

*Summary written by: Daniel T. Eitzman, MD*

## Aspirin in the Primary and Secondary Prevention of Vascular Disease: Collaborative Meta-Analysis of Individual Participant Data From Randomised Trials

Antithrombotic Trialists (ATT) Collaboration.
*Lancet* 2009;373:1849–1860.

**Study Question:** Low-dose aspirin is of definite and substantial net benefit for many people who already have occlusive vascular disease. What are the benefits and risks in primary prevention?

**Methods:** The authors conducted a meta-analysis of six primary prevention trials (95,000 individuals at low average risk, 660,000 person-years, 3,554 serious vascular events) and 16 secondary prevention trials (17,000 individuals at high average risk, 43,000 person-years, 3,306 serious vascular events) that compared long-term aspirin versus no aspirin. Primary endpoints were serious vascular events and major bleeds. Conclusions are based on an intention-to-treat analysis of first events during the scheduled treatment periods.

**Results:** Daily aspirin dose ranged from 75-500 mg, and one study gave 325 mg aspirin every other day. In the primary prevention trials, aspirin allocation yielded a 12% proportional reduction in serious vascular events, due mainly to a reduction of about a fifth in nonfatal MI, and no effect on coronary heart disease death. The net effect on stroke was not significant. Vascular mortality did not differ significantly. Aspirin allocation increased major gastrointestinal and extracranial bleeds (0.10% vs. 0.07% per year, $p < 0.0001$), and the main risk factors for coronary disease were also risk factors for bleeding. In the secondary prevention trials, aspirin allocation yielded a greater absolute reduction in serious vascular events (6.7% vs. 8.2% per year, $p < 0.0001$), with a nonsignificant increase in hemorrhagic stroke, but reductions of about a fifth in total stroke and in coronary events.

**Conclusions:** In primary prevention without previous disease, aspirin is of uncertain net value, as the reduction in occlusive events needs to be weighed against any increase in major bleeds. Further trials are in progress.

**Perspective:** Results of the US Physicians Health Study led to the present practice of low-dose aspirin in middle-aged and older men whose risk of bleeding is low and in whom the blood pressure is controlled. In contrast, results of the Women's Health Study led to guidelines suggesting aspirin for women 65 years and older for stroke prevention, and consideration of low-dose aspirin for women with an annual event rate estimated at >1%. There is good reason to continue studies to define optimal use of aspirin for primary prevention. Although counterintuitive, two recent studies did not demonstrate a value for low-dose aspirin for prevention of cardiovascular events in diabetes. We need a better and safer antiplatelet drug than aspirin for primary and secondary prevention. Of course it is not likely that any new agent will be as cost-effective.

*Summary written by: Melvyn Rubenfire, MD*

## Prevalence of Cardiovascular Disease Risk Factors Among National Football League Players

**Tucker AM, Vogel RA, Lincoln AE, et al.**
***JAMA* 2009;301:2111–2119.**

**Study Question:** What are the cardiovascular disease risk factors in active National Football League (NFL) players, and how do these compare with data from the CARDIA study?

**Methods:** Data from a cross-sectional study of 504 veteran football players from a convenience sample of 12 NFL teams at professional athletic training facilities between April and July 2007 were compared with men of the same age in the general US population (CARDIA study, a population-based observational study of 1,959 participants ages 23-35 years recruited in 1985-1986). The prevalence of cardiovascular risk factors was assessed in both groups.

**Results:** NFL players were less likely to smoke compared with the CARDIA group. Despite being taller and heavier, NFL players had significantly lower prevalence of impaired fasting glucose (6.7% [n = 24]; 95% CI, 4.6%-8.7%; vs. 15.5% [n = 267]; 95% CI, 13.8%-17.3%; $p < 0.001$). The groups did not differ in prevalence of high total cholesterol and low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C), or high triglycerides. Hypertension and prehypertension were significantly more common in NFL players than in the CARDIA group (both $p < 0.001$). Large size measured by body mass index (BMI) was associated with increased blood pressure, LDL-C, triglycerides, and fasting glucose; and decreased HDL-C.

**Conclusions:** Compared with a sample of healthy young-adult men, a sample of substantially larger NFL players had a lower prevalence of impaired fasting glucose, less reported smoking, a similar prevalence of dyslipidemia, and a higher prevalence of hypertension. Increased size was associated with increased cardiovascular risk factors.

**Perspective:** Over the past 30 years, there has been a significant increase in BMI of offensive and defensive NFL linemen; and in 2003, 26% of NFL players had a BMI ≥30 kg/m$^2$. There is debate about whether athletic fitness has a protective effect against the health risks of obesity. This study reveals that some cardiovascular risk factors are similar (dyslipidemia), some (impaired fasting glucose, tobacco use) occur at a lower rate among NFL players, and some (hypertension and prehypertension) occur at a higher rate. However, in this athletic population, the clinical cardiovascular implications are not known. Although this study also reveals that higher BMI is associated with more cardiovascular risk factors, it is also unknown what cardiovascular risk factors and events these men would suffer if they did or did not participate in professional football.

*Summary written by: David S. Bach, MD*

## Microalbuminuria and Risk of Venous Thromboembolism

**Mahmoodi BK, Gansevoort RT, Veeger GM, et al., on behalf of the Prevention of Renal and Vascular End-Stage Disease (PREVEND) Study Group.**
***JAMA* 2009;301:1790–1797.**

**Study Question:** Does the presence of microalbuminuria predispose to venous thromboembolism (VTE)?

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**Methods:** The authors presented data from PREVEND, a prospective community-based cohort study of residents of Groningen, the Netherlands, between the ages of 28-75, who were not pregnant or receiving insulin, followed in two cohorts: 1) those with urinary albumin concentration (UAC) >10 mg/L, and 2) those with UAC <10 mg/L. Data collection included risk factors for cardiovascular and renal disease. The main endpoint was symptomatic, verified VTE. Controls were 2,592 participants randomly selected from among those without microalbuminuria, and the exposure cohort was 6,000 individuals with UAC >10 mg/L.

**Results:** Among the 8,574 subjects were 129 episodes of VTE over a mean follow-up of 8.6 years, for an annual incidence of 0.14% (95% confidence interval [CI], 0.11-0.19%). The annual incidence ranged from 0.12% to 0.56% for participants having urinary albumin excretion (UAE) <15 versus UAE >300 mg/24-hour urine collection, respectively (p for trend < 0.001). Hazard ratio for VTE was 2.82 (95% CI, 1.21-6.61) for those with UAE >300 mg per 24 hours versus those having UAE <15 mg per 24 hours. Hazard ratio for VTE for those with microalbuminuria versus normal albuminuria (UAE <30 mg per 24 hours) was 2.0 (95% CI, 1.34-2.98; p < 0.001).

**Conclusions:** Microalbuminuria is independently associated with an increased risk of VTE.

**Perspective:** Although the CIs were somewhat wide, there appears to be a clear association between UAE and the risk for DVT. Importantly, this risk was 'dose' related, going up in a linear fashion with increasing concentrations of urinary albumin. It is increasingly well established that proteinuria is a risk factor for cardiovascular and arterial thrombotic events. These data extend this observation to VTE. Recent studies also demonstrated that lipid-lowering therapy may be associated with a decreased risk of VTE. It makes sense to include microalbuminuria as a risk factor in the assessment of cardiovascular as well as VTE risk. What remains to be seen is if therapy directed at the prevention or treatment of microalbuminuria—such as the use of angiotensin-converting enzyme inhibitors—will reduce incidence of VTE.

*Summary written by: James B. Froehlich, MD*

## Residual Thrombosis on Ultrasonography to Guide the Duration of Anticoagulation in Patients With Deep Venous Thrombosis

**Prandoni P, Prins MH, Lensing AW, et al., for the AESOPUS Investigators.**
***Ann Intern Med* 2009;150:577–585.**

**Study Question:** Can the results of ultrasound imaging be used to determine the length of anticoagulation therapy in patients with deep venous thrombosis (DVT)?

**Methods:** The authors reported a randomized, multicenter, open-label trial of fixed duration anticoagulation (3 months for warfarin for secondary thrombosis, or 6 months for unprovoked thrombosis) versus flexible duration, ultrasonography-directed anticoagulation (stop warfarin when veins recanalized on ultrasound). All study subjects had follow-up at 3, 9, 15, 21, and 33 months after randomization. Ultrasound imaging was performed at each visit for all subjects. For those subjects assigned to flexible duration of therapy, when venous recanalization was observed, anticoagulation therapy was discontinued up to a maximum duration of 9 (secondary DVT) or 21 (idiopathic DVT) months.

**Results:** Among the 538 consecutive outpatients with a first episode of acute proximal DVT, there were 46 (17.2%) patients in the fixed duration group and 32 (11.9%) flexible duration subjects that developed recurrent DVT. For the subsets of subjects with unprovoked DVT, or secondary DVT, the differences were not statistically significant. Major bleeding rates did not differ significantly between the fixed duration and flexible duration groups (two [0.7%] vs. four [1.5%], respectively).

**Conclusions:** Tailoring duration of anticoagulation for DVT on the basis of follow-up ultrasonography findings reduces the rate of recurrent venous thromboembolism (VTE) in adults suffering from proximal DVT.

**Perspective:** Current guidelines suggest at least considering lifelong anticoagulation in patients with even a single episode of VTE that is idiopathic. The current study suggests that waiting for recanalization prior to discontinuing anticoagulation therapy is associated with a decreased risk of recurrence during the time period studied. One major problem with this study, however, is that the length of follow-up after cessation of anticoagulants was shorter in the ultrasound group. Prior studies suggest that over a similar period of follow-up after cessation of therapy, those patients with ongoing risk factors tended to have similar rates of recurrence that were simply delayed after a longer period of therapy. Another shortcoming of this study is that it does not focus on the most important clinical question. The study mixed secondary and idiopathic DVT patients. The current literature would suggest that a short duration of therapy (3 months) is adequate and associated with low recurrence rates in patients with secondary DVT. Methods to determine duration of therapy for patients with idiopathic or unprovoked DVT are needed, however, given the reticence of most patients and clinicians to recommend or undergo lifelong anticoagulation.

*Summary written by: James B. Froehlich, MD*