is consistent with the results of the Framingham Offspring Study (no association between interleukin-6 or CRP and new-onset AF). Taken together, these studies suggest that inflammation may contribute to the generation of AF in some patients, but is unlikely to be a major determinant of recurrences in the general population of AF patients.

**Summary written by:** Fred Morady, MD

---

**Arrhythmias**

**Predicting Atrial Fibrillation Recurrence With Circulating Inflammatory Markers in Patients in Sinus Rhythm at High Risk for Atrial Fibrillation: Data From the GISSI Atrial Fibrillation Trial**


**Study Question:** Are markers of inflammation predictive of recurrent atrial fibrillation (AF)?

**Methods:** Interleukin-6, high-sensitivity C-reactive protein (hs-CRP), and pentraxin-3 plasma concentrations were measured at baseline and 6 and 12 months of follow-up in 382 patients (mean age 68 years) with a history of AF. Episodes of AF during follow-up were detected by symptoms or weekly transtelephonic monitor recordings.

**Results:** AF recurred at least once during follow-up in 53% of patients. Baseline median concentrations of the three inflammatory markers did not differ significantly between patients with and without recurrent AF during follow-up. None of the three inflammatory markers by themselves or in combination were significant predictors of recurrent AF.

**Conclusions:** Inflammatory markers are not predictive of recurrent AF in patients with a history of AF.

**Perspective:** Several small studies have demonstrated that inflammatory markers such as hs-CRP are predictive of recurrent AF after cardioversion or radiofrequency catheter ablation of AF. The present study had a larger sample size and included patients at high risk of recurrent AF. This study is consistent with the results of the Framingham Offspring Study (no association between interleukin-6 or CRP and new-onset AF). Taken together, these studies suggest that inflammation may contribute to the generation of AF in some patients, but is unlikely to be a major determinant of recurrences in the general population of AF patients.

**Summary written by:** Fred Morady, MD

**Chest-Compression-Only Versus Standard Cardiopulmonary Resuscitation: A Meta-Analysis**


**Study Question:** Does chest-compression-only resuscitation (CCOR) improve outcomes compared to conventional cardiopulmonary resuscitation (CCPR)?

**Methods:** This was a meta-analysis of three randomized clinical trials (RCTs) and seven observational cohort studies in which bystanders were instructed to perform either CCOR or CCPR after reporting an out-of-hospital cardiac arrest (OHCA). The primary outcome was survival to hospital discharge.

**Results:** In the RCTs, the overall sample sizes were 1,500 in the CCOR group and 1,531 in the CCPR group. Survival to hospital discharge was significantly higher in the CCOR (14%) than the CCPR (12%) group. In the nonrandomized cohort studies, the overall sample sizes were 2,731 in the CCOR group and 11,152 in the CCPR group. Survival to hospital discharge was 8% in both groups.
**Conclusions:** Compared to CCPR, CCOR by bystanders improves survival in victims of OHCA.

**Perspective:** This study demonstrates the value of a meta-analysis when a therapeutic effect is modest. Although survival to hospital discharge tended to be higher with CCOR than CCPR in the three RCTs, the difference was not significant in any of the studies. By meta-analysis of the three studies, a significant improvement in outcomes with CCOR was demonstrated. Although modest, an absolute increase in survival of 2% with bystander CCOR for OHCA translates to a few thousand lives saved per year.

*Summary written by: Fred Morady, MD*

---

**Metoprolol Versus Amiodarone in the Prevention of Atrial Fibrillation After Cardiac Surgery: A Randomized Trial**


**Study Question:** Is metoprolol as effective as amiodarone for preventing post-cardiac surgery atrial fibrillation (AF)?

**Methods:** In this prospective study, 316 patients (mean age 64 years) with no history of AF underwent on-pump coronary artery bypass grafting and/or aortic valve surgery. The patients were randomly assigned to receive a 48-hour infusion of metoprolol (n = 159), 1-3 mg/h depending on heart rate, or amiodarone (n = 157), 15 mg/kg/d with maximum of 1000 mg/24 h, starting 15-20 hours after the operation. Continuous electrocardiographic monitoring was performed and the primary endpoint was the first episode of AF lasting >5 minutes.

**Results:** A similar percentage of patients experienced AF in the metoprolol (23.9%) and amiodarone (24.8%) groups. However, because of large confidence intervals, a significant difference between the two groups could not be ruled out. The mean duration of hospitalization was 5.5 days and did not differ significantly between groups.

**Conclusions:** Prophylactic therapy with metoprolol or amiodarone results in a similar risk of AF after cardiac surgery, but this study was underpowered to exclude a significant difference in efficacy.

**Perspective:** This study strongly suggests that a significant difference in efficacy would be minor in magnitude. This is consistent with published meta-analyses in which metoprolol and amiodarone reduced the risk of postoperative AF by 61% and 62%, respectively. The data validate the current recommendation of the European Association for Cardiothoracic Surgery to reserve amiodarone for patients in whom beta-blocker therapy fails or cannot be used.

*Summary written by: Debabrata Mukherjee, MD*

---

**Cardiovascular Surgery**

**Aspirin Plus Clopidogrel Versus Aspirin Alone After Coronary Artery Bypass Grafting: The Clopidogrel After Surgery for Coronary Artery Disease (CASCADE) Trial**


**Study Question:** What is the effect of the addition of clopidogrel to aspirin in inhibiting saphenous vein graft (SVG) disease after coronary artery bypass grafting (CABG)?

**Methods:** In CASCADE, a double-blind phase II trial, 113 patients undergoing CABG with SVGs were randomized to receive aspirin 162 mg plus clopidogrel 75 mg daily or aspirin 162 mg plus placebo daily for 1 year. The primary outcome was SVG intimal hyperplasia, as determined by intravascular ultrasound at 1 year. Secondary outcomes were graft patency, major adverse cardiovascular events, and major bleeding. One-year intravascular ultrasound and coronary angiography were performed in 92 patients (81.4%).

**Results:** SVG intimal area did not differ significantly between groups (4.1 ± 2.0 vs. 4.5 ± 2.1 mm², aspirin-clopidogrel vs. aspirin-placebo, respectively; p = 0.44). Overall 1-year graft patency was 95.2% versus 95.5%, and SVG patency was 94.3% versus 93.2% (p = 0.69). Freedom from major adverse cardiovascular events at 1 year was 92.9 ± 3.4% in the aspirin-clopidogrel and 91.1 ± 3.8% in the aspirin-placebo group (p = 0.76). The incidence of major bleeding at 1 year was similar for the two groups (1.8% vs. 0%, p = 0.50).

**Conclusions:** Compared with aspirin monotherapy, the combination of aspirin plus clopidogrel did not significantly reduce the process of SVG intimal hyperplasia after CABG. However, the study was underpowered to exclude a significant difference in efficacy.

**Perspective:** This study strongly suggests that a significant difference in efficacy would be minor in magnitude. This is consistent with published meta-analyses in which metoprolol and amiodarone reduced the risk of postoperative AF by 61% and 62%, respectively. The data validate the current recommendation of the European Association for Cardiothoracic Surgery to reserve amiodarone for patients in whom beta-blocker therapy fails or cannot be used.

*Summary written by: Debabrata Mukherjee, MD*

---

**Congenital Heart Disease**

**Mortality Resulting From Congenital Heart Disease Among Children and Adults in the United States, 1999 to 2006**
Study Question: What are the temporal trends of mortality resulting from congenital heart disease from 1999 to 2006?

Methods: Death certificate data filed in the United States from 1999 to 2006 were used to calculate annual congenital heart disease mortality by age at death, race-ethnicity, and sex. For individuals ≥1 year of age, population counts from the US Census were used, whereas live birth rates were used to calculate infant mortality.

Results: Over the study period, 41,494 congenital heart disease-related deaths and 27,960 deaths resulting from congenital heart disease (age standardized mortality rates, 1.78 and 1.20 per 100,000, respectively) occurred. There was an overall decline in congenital heart disease mortality of 24.1% over the study period. While age-related mortality declined among all race-ethnicities studied, overall and infant mortality was higher among non-Hispanic blacks compared with non-Hispanic whites. Infant mortality accounted for 48% of all mortality resulting from congenital heart disease.

Conclusions: Mortality from congenital heart disease continues to decline in children and adults, with persistent differences between race-ethnicities. Although mortality in infancy continues, late mortality is significant, emphasizing the importance of infrastructure for the care of adults with congenital heart disease.

Perspective: This study is among a series of papers published over the last several months investigating changing patterns of mortality in congenital heart disease. In the current paper, Gilboa, et al. reported steady improvement in survival in all age groups over a relatively short time course (1999-2006). This study showed a strikingly higher proportion of deaths occurring in infancy (48%) in the most recent surgical era than the Canadian study (<5%); the reasons are unclear and deserve further study. All studies agree that more infants and children with congenital heart disease are surviving to adulthood, and that the medical community will need to prepare for the care of more adults with more complex congenital heart disease.

Summary written by: Timothy B. Cotts, MD

General Cardiology

n–3 Fatty Acids and Cardiovascular Events After Myocardial Infarction

Kromhout D, Gilillat EJ, Geleijmse JM, et al., on behalf of the Alpha Omega Trial Group.

Study Question: What is the effect of the marine n–3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and of the plant-derived alpha-linolenic acid (ALA) on the rate of cardiovascular events (CVEs) in persons who have had a myocardial infarction (MI)?

Methods: Alpha Omega Alpha was a multicenter, double-blind, placebo-controlled trial conducted over 4 years, that randomly assigned 4,837 patients, ages 60-80 years, who have had an MI and were receiving antihypertensive (89.7%), antithrombotic (97.5%), and lipid-modifying (86.0%) therapy. Subjects were randomized to one of four trial margarines supplemented with the following: a combination of EPA+DHA (400 mg of EPA+DHA), ALA (2 g of ALA), EPA+DHA and ALA, or a placebo margarine. The primary endpoint was the rate of major CVEs, which comprised fatal and nonfatal CVEs and cardiac interventions. Data were analyzed according to intention-to-treat, with Cox proportional-hazards models.

Results: Mean age was 69 years and 78% were men, 16.9% smokers, 24% obese, and 21% diabetics. The median period between MI and entry was 3.7 years. Patients consumed, on average, 18.8 g of margarine per day, which resulted in additional intakes of 226 mg of EPA+150 mg of DHA, 1.9 g of ALA, or both, in the active-treatment groups. With a median follow-up of 40.8 months and 15,531 patient-years, a major CVE occurred in 671 patients (13.9%). Neither EPA+DHA nor ALA reduced the primary endpoint. In the prespecified subgroup of women, ALA, as compared with placebo and EPA+DHA alone, was associated with a reduction in the rate of major CVEs that approached significance (hazard ratio, 0.73; 95% CI, 0.51-1.03; p = 0.07). Adverse events did not differ significantly among groups.

Conclusions: Low-dose supplementation with EPA+DHA or ALA did not significantly reduce the rate of major CVEs among patients who have had an MI and who were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy.

Perspective: Observational studies and randomized trials suggest a protective effect of marine sources of omega-3 fatty acids in persons with cardiovascular disease. This trial was well designed and appropriately powered based upon available evidence. Why was it negative? The most likely reason is the relative weak effect of EPA+DHA in patients on evidence-based treatments. The effect of high-dose EPA+DHA (1000-4000 mg) needs to be assessed prior to concluding a lack of benefit.

Summary written by: Melvyn Rubenfire, MD

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators.

Study Question: What is the efficacy and safety of rivaroxaban compared with standard therapy consisting of enoxaparin and a vitamin K antagonist in patients with acute, symptomatic
deep-vein thrombosis (DVT)?

**Methods:** The EINSTEIN–DVT investigators conducted an open-label, randomized, event-driven, noninferiority study that compared oral rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with subcutaneous enoxaparin, followed by a vitamin K antagonist (either warfarin or acenocoumarol) for 3, 6, or 12 months in patients with acute, symptomatic DVT. In parallel, they carried out a double-blind, randomized, event-driven superiority study (EINSTEIN–Extension) that compared rivaroxaban alone (20 mg once daily) with placebo for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism. The primary efficacy outcome for both studies was recurrent venous thromboembolism. The principal safety outcome was major bleeding or clinically relevant nonmajor bleeding in the initial-treatment study and major bleeding in the continued-treatment study.

**Results:** The study of rivaroxaban for acute DVT included 3,449 patients: 1,731 given rivaroxaban and 1,718 given enoxaparin plus a vitamin K antagonist. Rivaroxaban had noninferior efficacy with respect to the primary outcome (36 events [2.1%] vs. 51 events with enoxaparin–vitamin K antagonist [3.0%]; p < 0.001). The principal safety outcome occurred in 8.1% of the patients in each group. In the continued-treatment study, which included 602 patients in the rivaroxaban group and 594 in the placebo group, rivaroxaban had superior efficacy (8 events [1.3%] vs. 42 with placebo [7.1%]; p < 0.001). Four patients in the rivaroxaban group had nonfatal major bleeding (0.7%) versus none for placebo (p = 0.11).

**Conclusions:** Rivaroxaban offers a simple, single-drug approach to the short-term and continued treatment of venous thrombosis.

**Perspective:** This study suggests that rivaroxaban alone is as effective as standard therapy, with similar safety, for the treatment of acute DVT, and that when treatment is continued, rivaroxaban is very effective in preventing recurrences, and has an acceptable risk of bleeding. Furthermore, a prespecified indicator of net clinical benefit (symptomatic recurrent venous thromboembolism plus major bleeding) favored rivaroxaban.

**Summary written by:** Debabrata Mukherjee, MD

---

**Association of Troponin T Detected With a Highly Sensitive Assay and Cardiac Structure and Mortality Risk in the General Population**


**Study Question:** What are the prevalence and determinants of detectable cardiac troponin T (cTnT) in the population, and are cTnT levels associated with pathological cardiac phenotypes and subsequent mortality?

**Methods:** cTnT levels were measured using both the standard and the highly sensitive assays in 3,546 individuals ages 30-65 years enrolled between 2000 and 2002 in the Dallas Heart Study, a multiethnic, population-based cohort study. Mortality follow-up was complete through 2007. Participants were placed into five categories based on cTnT levels. Magnetic resonance imaging measurements of cardiac structure and function and mortality through a median of 6.4 years of follow-up were performed.

**Results:** In Dallas County, the prevalence of detectable cTnT (≥0.003 ng/ml) was 25.0% with the highly sensitive assay versus 0.7% with the standard assay. Prevalence was 37.1% in men versus 12.9% in women and 14.0% in participants younger than 40 years versus 57.6% in those 60 years and older. Prevalence of left ventricular hypertrophy increased from 7.5% in the lowest cTnT category (<0.003 ng/ml) to 48.1% in the highest (≥0.014 ng/ml) (p < 0.001); prevalence of left ventricular systolic dysfunction and chronic kidney disease also increased across categories (p < 0.001 for each). During the 6.4 years, there were 151 total deaths, including 62 cardiovascular disease deaths. All-cause mortality increased from 1.9% to 28.4% across higher cTnT categories (p < 0.001).

**Conclusions:** In this population-based cohort, cTnT detected with a highly sensitive assay was associated with structural heart disease and subsequent risk for all-cause mortality.

**Perspective:** The study suggests that circulating cTnT is detectable in ~25% of adults ages 30–65 years in the general population using a highly sensitive assay, and higher levels of cTnT are associated with cardiac structural abnormalities including left ventricular hypertrophy and left ventricular systolic dysfunction. Since this assay detects cTnT in a significant proportion of the general population, it is possible that widespread application may expose some patients presenting with noncardiac chest pain to unnecessary risk and expense of invasive cardiac procedures. A higher threshold to diagnose myocardial infarction may need to be set when using these assays.

**Summary written by:** Debabrata Mukherjee, MD

---

**Heart Failure/Transplant**

**Telemonitoring in Patients With Heart Failure**


**Study Question:** Does telephone-based computerized monitoring improve outcomes in subjects with heart failure (HF)?

**Methods:** This was a multicenter randomized study of telemonitoring versus usual care in higher risk subjects with
systolic and/or diastolic HF. All subjects had been hospitalized within 30 days and individuals unable to participate in telemonitoring were excluded. Subjects randomized to telemonitoring were instructed to call a toll-free commercial telemonitoring system daily to answer HF-related questions. Telemonitoring information was reviewed by site coordinators daily with “triggered variances” in subject answers sent to clinicians for review. Patient and clinician adherence with the protocol were monitored. The primary outcome was death or all-cause hospitalization within 180 days of enrollment.

**Results:** Of the 5,069 patients screened, 826 underwent randomization to telemonitoring (n = 826) versus usual care (n = 827). Baseline characteristics were similar between groups. Mean patient age was 61 years, 86% were New York Heart Association class II or III, mean creatinine was 1.5 mg/dl, 39% were black, 42% were female, and 71% had a left ventricular ejection fraction <40%. Mean household income was <$10,000 in 28% and 24% did not graduate from high school. At least one call during the 180-day study was made by 86% of telemonitoring patients. Patient adherence to the protocol decreased during the study (90% at 1 week and 55% by 26 weeks). Mortality was 11% in both groups at 180 days. There were no differences between groups in total readmissions (49% telemonitoring vs. 47% control) or HF-related readmissions (28% telemonitoring vs. 27% control). The hazard ratio for the primary endpoint (death/rehospitalization) was 1.04; 95% confidence interval, 0.91-1.19).

The hazard ratio for the primary endpoint (death/rehospitalization) was 1.04; 95% confidence interval, 0.91-1.19). The hazard ratio for the primary endpoint (death/rehospitalization) was 1.04; 95% confidence interval, 0.91-1.19).

**Conclusions:** Telemonitoring did not improve outcomes in patients recently hospitalized with HF.

**Perspective:** Readmission percentages and mortality in this study were on target with previously published HF studies. Thus, it appears that this form of telemonitoring does not impact short-term outcomes in patients with these clinical characteristics. The decline in adherence to patient-initiated telemangement was impressive. Perhaps alternative methods of telemonitoring that remove the onus from the patient would be more effective. Overall, there is much heterogeneity in study results on HF telemangement due to the heterogeneity of the patients studied across studies (wide confidence intervals). Also, power was limited (30-day mortality was <3%). The authors hypothesize that BNP testing may impact hospital stay lengths by allowing for faster implementation of appropriate therapies in those with dyspnea (i.e., diuretics in those with heart failure).

**Summary written by:** Jennifer Ann Cowger, MD

---

**Meta-Analysis: Effect of B-Type Natriuretic Peptide Testing on Clinical Outcomes in Patients With Acute Dyspnea in the Emergency Setting**


**Study Question:** Does B-type natriuretic peptide (BNP) or N-terminal BNP (NT-BNP) testing in patients presenting to the emergency room (ER) with acute dyspnea impact outcomes?

**Methods:** This was a meta-analysis examining published (January 1996-July 2010) randomized controlled trials that evaluated the use of BNP or NT-BNP testing in patients presenting with acute dyspnea to the ER. Cochrane Collaboration methodological guidelines were used to assess study quality for study inclusion. Outcomes included mortality (mainly 30-day), admissions, and/or length of hospital stay.

**Results:** Five trials encompassing 2,513 patients were included. Physicians in four of five of these trials were blinded to BNP results in the control group. Trial designs and patients enrolled were very heterogeneous. ER-based BNP testing provided no impact on all-cause mortality (95% confidence interval [CI], 0.65-1.4). Trends toward reduced admissions were noted with BNP testing (CI, 0.67-1.01). Lengths of stay were significantly reduced (95% CI, -2.3 to -0.14 days) with BNP testing.

**Conclusions:** BNP testing in the ER led to reduced length of stay, but had no impact on mortality and no significant impact on admissions.

**Perspective:** The major, but not surprising, finding from this study is heterogeneity. It does not appear that ER-based BNP testing impacts mortality, but may impact admission rates. The lack of mortality significance again likely relates to the heterogeneity of the patients studied across studies (wide confidence intervals). Also, power was limited (30-day mortality was <3%). The authors hypothesize that BNP testing may impact hospital stay lengths by allowing for faster implementation of appropriate therapies in those with dyspnea (i.e., diuretics in those with heart failure).

**Summary written by:** Jennifer Ann Cowger, MD

---

**Prevention/Vascular**

**Maintaining a High Physical Activity Level Over 20 Years and Weight Gain**


**Study Question:** What is the relationship between habitual activity levels and changes in body mass index (BMI) and waist circumference over 20 years?

**Methods:** The Coronary Artery Risk Development in Young Adults (CARDIA) study is a prospective longitudinal study with 20 years of follow-up (1985-1986 to 2005-2006). Habitual activity was defined as maintaining high, moderate, and low activity levels based on sex-specific tertiles of activity scores at baseline. Participants comprised a population-based multicenter cohort of 3,554 men and women.
A total of 70 randomized controlled trials (with 324,168 participants) were included in this meta-analysis. Mean follow-up was 3.5 years. In the fixed-effect models, no differences were observed for ARBs (odds ratio [OR], 1.01), ACEi (OR, 1.00), beta-blockers (OR, 0.97), CCBs (OR, 1.05), diuretics (OR, 1.00), or other controls (OR, 0.97). An increased cancer risk was observed for the combination of ARBs plus ACEi (OR, 1.14). This risk was not observed in the random-effects model (OR, 1.5). Regarding cancer-related deaths, no differences were observed for ARBs (OR, 1.00), ACEi (OR, 0.95), beta-blockers (OR, 0.93), CCBs (OR, 0.96), diuretics (OR, 0.98), other controls (OR, 1.08), and ACEi plus ARBs (95% CI, 0.90–1.32).

Conclusions: Risk of cancer or cancer-related deaths was not increased with the use of ARBs, ACEi, beta-blockers, diuretics, and CCBs. However, an increased risk of cancer with the combination of ACEi and ARBs could not be ruled out.

Perspective: This meta-analysis provides extensive evidence that antihypertensive medications in general do not increase risk for cancer or cancer mortality. It is not clear if the combination of ARBs plus ACEi does in fact increase cancer risk; however, such a combination is not generally first-line therapy in the management of hypertension.

Summary written by: Elizabeth A. Jackson, MD

Guidelines for the Primary Prevention of Stroke. A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association


Perspective: The following are 10 points to remember about these guidelines:

1: Approximately 795,000 people in the United States have a stroke each year, and stroke is the third leading cause of deaths annually. Although the death rate for stroke fell by 33.5% over the past 10 years, stroke incidence may be increasing.

2: Stroke prevention efforts can reduce incidence by 50%, and a healthy lifestyle is associated with an 80% lower risk of a first stroke. The first goal should be to identify persons at high risk for stroke including those with nonmodifiable risk factors for whom more intense treatment of modifiable risk factors may be indicated.

3: Nonmodifiable risk factors include age (strokes double for each decade over 55 years); men; Blacks and Hispanic/Latino Americans; and family history of strokes (e.g., ischemic or intracranial hemorrhage from aneurysms). Noninvasive screening of first-degree relatives of persons with subarachnoid hemorrhage or intracranial aneurysms is not indicated.

4: Modifiable risk factors for stroke include smoking (odds ratio [OR], 1.9), hypertension (age-related OR, 8.0), diabetes
(OR, 1.8–6 blood pressure dependent), markedly elevated cholesterol (OR, 1.5), low high-density lipoprotein cholesterol (OR, 2.0), atrial fibrillation (age-related OR, 2.6–4.5), asymptomatic carotid stenosis (OR, 2.0), sickle cell (OR, >200), estrogens (OR, 1.4), physical inactivity (OR, 2.7), and obesity (OR, 1.4 per 5 kg/m² increase in body mass index).

5: Potentially modifiable risk factors include migraine with an aura, the metabolic syndrome, >4 drinks of alcohol per day, drug abuse, hyperhomocysteinemia, increased lipoprotein (a), hypercoagulability, and inflammatory diseases of all types.

6: Hypertension is the most important modifiable risk factor. There is a lower stroke rate in patients with a blood pressure target of <120 mm Hg than <140 mm Hg. The blood pressure goal is <140/90 mm Hg, and <130/80 mm Hg in diabetics and those with chronic kidney disease.

7: Treatment of diabetics for stroke prevention should include a statin, and an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker. The benefit of aspirin for stroke risk reduction has not been demonstrated in diabetics, but should be considered in those with high cardiovascular disease risk.

8: Treatment of dyslipidemias for stroke prevention should include a statin in persons at high risk for coronary heart disease and diabetes, possibly in combination with niacin in patients with a low high-density lipoprotein cholesterol or elevated lipoprotein (a).

9: Adjusted-dose warfarin (target international normalized ratio, 2.0-3.0) is recommended for all patients with nonvalvular atrial fibrillation deemed to be at high risk and those at moderate risk who are at low risk for warfarin. Antiplatelet therapy with aspirin is indicated in atrial fibrillation at low risk or at moderate risk with patient preference or increased risk for warfarin. Dual antiplatelet therapy is warranted in high-risk patients unsuitable for warfarin.

10: Carotid artery stenosis is clinically and hemodynamically significant at a reduction in luminal diameter of >70% on validated duplex, or >80% on computed tomography angiography or magnetic resonance angiography. Patients with carotid stenosis should be treated with lifestyle change and medical therapy. Population screening for asymptomatic carotid disease is not recommended.

### Summary written by: Melvyn Rubenfire, MD

### Lifetime Fruit and Vegetable Consumption and Arterial Pulse Wave Velocity in Adulthood: The Cardiovascular Risk in Young Finns Study


**Study Question:** Are childhood and young adulthood lifestyle risk factors determinants of pulse-wave velocity (PWV) in adults?

**Methods:** The study cohort was comprised of 1,622 subjects of the Cardiovascular Risk in Young Finns Study followed up for 27 years from baseline (1980; ages 3–18 years) with lifestyle risk factor data available since childhood. Arterial PWV was measured in 2007 by whole-body impedance cardiography.

**Results:** Mean age at baseline was 10.5 ± 5.0 years, and 54.5% were women. Dietary patterns remained stable from childhood to adulthood, and especially among older subjects. These patterns were also associated with cardiovascular risk factors. Vegetable consumption in childhood was inversely associated with adulthood PWV (p = 0.02), and this association remained significant (p = 0.004) when adjusted for traditional risk factors. Vegetable consumption was also an independent predictor of PWV in adulthood when adjusted for lifestyle or traditional risk factors (p = 0.002 and p = 0.0007, respectively). Persistently high consumption of both fruits and vegetables from childhood to adulthood was associated with lower PWV compared with persistently low consumption (p = 0.03 for both). The number of lifestyle risk factors in childhood was directly associated with PWV in adulthood (p = 0.001). This association remained significant when adjusted for the number of lifestyle risk factors in adulthood (p = 0.003).

**Conclusions:** These findings suggest that lifestyle risk factors, with low consumption of fruits and vegetables in particular, are related to arterial stiffness in young adulthood.

**Perspective:** Arterial PWV is a marker of central arterial stiffness and is an independent predictor of cardiovascular events and all-cause mortality. The findings strongly support the recommendations of a healthy lifestyle in children and young adults including a diet high in fruits, vegetables, and fiber; regular exercise; and avoidance of tobacco, each of which can prevent arterial stiffness associated with increasing age.

**Summary written by:** Melvyn Rubenfire, MD

### Effects of Aerobic and Resistance Training on Hemoglobin A₁C Levels in Patients With Type 2 Diabetes: A Randomized Controlled Trial


**Study Question:** What are the benefits of aerobic training alone, resistance training alone, and the combination of both on hemoglobin A₁C (HbA₁C) in individuals with type 2 diabetes?

**Methods:** A randomized controlled trial was conducted in 262 sedentary men and women with type 2 diabetes and HbA₁C
levels of 6.5% or higher. Participants were randomized to one of the three exercise protocols for 9 months between April 2007 and August 2009. Exercise intensity was 50-80% of maximum oxygen consumption with an aerobic dose of 12 kcal/kg/wk for the aerobic group and 10 kcal/kg/wk for the combination exercise group.

**Results:** A total of 63% were women and 47.3% were non-white. Mean age was 55.8 years, mean duration of diabetes was 7.1 years, mean body mass index was 34.9 kg/m², and baseline HbA₁c level was 7.7%; 97% were on one or more hypoglycemic agents, 18% of which included insulin. Compared with the control group, the absolute mean change in HbA₁c in the combination training exercise group was −0.34%. The mean changes in HbA₁c were not statistically significant in either the resistance training or aerobic training groups. Only the combination exercise group improved maximum oxygen consumption (mean, 1.0 ml/kg/min) compared with controls. All exercise groups reduced waist circumference from −1.9 to −2.8 cm compared with controls. The resistance training group lost a mean of −1.4 kg fat mass and combination of aerobic and resistance training compared with controls. The resistance training group lost a mean of −1.7 compared with controls.

**Conclusions:** Among patients with type 2 diabetes mellitus, a combination of aerobic and resistance training compared with the nonexercise control group improved HbA₁c levels. This was not achieved by aerobic or resistance training alone.

**Perspective:** This well-designed study strongly supports the 2008 Physical Activity Guidelines recommendation that optimal physical activity programs consist of regular physical activity combined with resistance training. To achieve the goal kcal/kg/wk, participants exercised about 150 minutes per week. Considering the added benefit on other cardiovascular risk factors, quality of life, and other clinical endpoints, consideration should be given to a cost-effective strategy for providing supervised exercise for diabetics.

*Summary written by: Melvyn Rubenfire, MD*

### Intensive Lowering of LDL Cholesterol With 80 mg Versus 20 mg Simvastatin Daily in 12,064 Survivors of Myocardial Infarction: A Double-Blind Randomised Trial


**Study Question:** Does more intensive statin therapy improve total and cardiovascular outcome following a myocardial infarction (MI), and if so at what risk?

**Methods:** SEARCH is a double-blind randomized trial in 12,064 men and women ages 18–80 years with a history of MI. Participants were either currently on or had clear indication for statin therapy, and had a total cholesterol concentration of at least 135 mg/dl if already on a statin or 175 mg/dl if not. Randomization to either 80 mg or 20 mg simvastatin daily was done centrally using a minimization algorithm. An additional placebo-controlled trial tested the efficacy of vitamin B12 + folic acid for lowering homocysteine. Participants were assessed at 2, 4, 8, and 12 months after randomization and then every 6 months until final follow-up. The primary endpoint was major vascular events, defined as coronary death, MI, stroke, or arterial revascularization.

**Results:** A total of 6,031 participants were allocated 80 mg simvastatin daily, and 6,033 were allocated 20 mg simvastatin daily; 84% were men and average age was 64.2 years. Nearly 75% were taking a statin prior to entry. During a mean follow-up of 6.7 years, allocation to 80 mg simvastatin produced an average 1.5 mg/dl greater reduction in low-density lipoprotein cholesterol (LDL-C) compared with 20 mg. Major vascular events occurred in 1,477 (24.5%) participants allocated 80 mg simvastatin versus 1,553 (25.7%) allocated 20 mg, corresponding to a 6% proportional reduction. There were no apparent differences in numbers of hemorrhagic strokes or deaths attributed to vascular or nonvascular causes. An insignificantly lower number of cancers occurred on 80 mg simvastatin. Compared with two (0.03%) cases of myopathy in patients taking 20 mg simvastatin daily, there were 53 (0.9%) cases in the 80 mg group, of whom 2/1,000 had a creatine kinase 40x ULN.

**Conclusions:** The 6% reduction in major vascular events with a further 1.5 mg/dl reduction in LDL-C in the SEARCH trial is consistent with previous trials. Myopathy was increased with 80 mg simvastatin daily, but intensive lowering of LDL-C can be achieved safely with other regimens.

**Perspective:** The large SEARCH trial offers further confirmation that higher statin doses and lower levels of LDL-C achieved improve outcome. The disappointingly modest further reduction in cardiovascular events from 80 mg versus 40 mg of simvastatin has several potential explanations. Most importantly nearly 75% were on statins, which biases against being able to demonstrate efficacy, and the 80 mg dose of simvastatin provided only a 6% further reduction in LDL-C than the 20 mg dose. I agree with the authors, who concluded lower is better and that better alternatives for efficacy and safety to 80 mg simvastatin include atorvastatin 80 mg, rosuvastatin 20–40 mg, or simvastatin + other cholesterol-lowering agents that do not increase the risk of myopathy.

*Summary written by: Melvyn Rubenfire, MD*