

# Advancing Evidence-Based Practice

## A Quarterly Compilation of Research Updates Most Likely to Change Clinical Practice

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### **CARDIAC SURGERY**

#### **Early Surgery Reduces Embolic Events in Selected Patients With Native Valve Infective Endocarditis**

The optimal timing for surgery for patients with native valve infective endocarditis remains under debate. In a study of 76 patients with left-sided endocarditis, severe valve disease, and vegetation >10 mm in diameter (mean age 47 years), the Early Surgery Versus Conventional Treatment in Infective Endocarditis (EASE) randomized trial compared early surgical intervention (within 48 hours of randomization; median time of 24 hours from randomization) vs antibiotic standard care. The standard care group's treatment was based on American College of Cardiology/American Heart Association guidelines [Circulation 2008 Oct 7;118(15):e523]: Surgery was performed only if urgent complications or symptoms persisted after antibiotic therapy. In the standard care group, 69% (27 patients) had urgent surgery at median 6.5 days after randomization, and 3 patients had elective surgery more than 2 weeks after randomization. At 6-week follow-up, no embolic events had occurred in the early surgery group compared to 21% in the standard care group ( $P=0.005$ , number needed to treat [NNT] 5) (level 1 [likely reliable] evidence), but no significant differences occurred in in-hospital mortality (3% [early surgery] vs 3% [standard care]). No additional embolic events were noted in either group at 6-month follow-up, and all-cause mortality was 3% (early surgery) vs 5% (standard care) (not significant). Endocarditis recurrence rates were similar between groups (0% [early surgery] vs 3% [standard care], not significant) [N Engl J Med 2012 Jun 28;366(26):2466].

### **CARDIOLOGY**

#### **Prehospital Epinephrine Appears to Increase Return of Spontaneous Circulation but Decrease 1-Month Survival in Patients With Out-of-Hospital Cardiac Arrest**

Epinephrine is a common early treatment for patients with out-of-hospital cardiac arrest and is part of the standard treatment algorithm recommended by

the American Heart Association [Circulation 2010 Nov 2;122(18 Suppl):S640]. However, a large cohort study in Japan questions current recommendations and suggests that prehospital epinephrine treatment may be harmful. A total of 417,188 patients (mean age 72 years) with out-of-hospital cardiac arrest from 2005 to 2008 were included in the study. Of this group, 15,030 patients (3.6%) were treated with intravenous epinephrine prior to hospital arrival. The investigators used a propensity analysis to control for confounding factors and selection bias, and a subgroup of 26,802 patients (half of whom received epinephrine) were included in the propensity-matched analysis. In the propensity-matched cohort, spontaneous circulation returned before hospital arrival in 18.3% of epinephrine-treated patients and 10.5% of nontreated patients ( $P<0.001$ , NNT 13) (level 2 [mid-level] evidence). However, 1-month survival was significantly reduced in the epinephrine group compared to the nontreated group (5.1% vs 7%, respectively,  $P<0.001$ , number needed to harm [NNH] 52). Survival with good or moderate cerebral performance at 1 month was also reduced for the epinephrine compared to the nontreated group (1.3% vs 3.1%, respectively,  $P<0.001$ , NNH 55). Similar results were attained in analyses of the complete cohort [JAMA 2012 Mar 21;307(11):1161]. Important note: This study looked at the effects of epinephrine use in the prehospital setting only, and findings should not be considered generalizable to the broader use of epinephrine.

### **COLON AND RECTAL SURGERY**

#### **Flexible Sigmoidoscopy Reduces Colorectal Cancer Incidence and Mortality Compared to Usual Care**

The optimal method of screening patients at average risk for colorectal cancer has yet to be determined. To evaluate the efficacy of flexible sigmoidoscopy screening, 154,900 patients aged 55-74 years were randomized to screening with flexible sigmoidoscopy vs usual care from 1993-2001 as part of the Prostate, Lung, Colorectal, and Ovarian (PLCO)

**Level 1 [likely reliable] Evidence:** research results addressing clinical outcomes and meeting an extensive set of quality criteria that minimize bias.

**Level 2 [mid-level] Evidence:** research results addressing clinical outcomes and using some method of scientific investigation, but not meeting the quality criteria to achieve level 1 evidence labeling.

**Level 3 [lacking direct] Evidence:** reports that are not based on scientific analysis of clinical outcomes. Examples include case series, case reports, expert opinion, and conclusions extrapolated indirectly from scientific studies.

Cancer Screening Trial. The sigmoidoscopy group was offered screening at baseline (83.5% were screened) and 3-5 years later (54% had repeat screening). Patients with a positive screen (detection of polyp or mass) were referred for additional diagnostic consultation (5.5% during the first 5 years and 47.7% after the screening phase). In the usual care group, 46.5% had either flexible sigmoidoscopy or colonoscopy during the screening phase, and 48% had routine colonoscopy after the screening phase. Median follow-up was 11.9 years. Colorectal cancer occurred in 1.31% of patients in the flexible sigmoidoscopy group vs 1.66% in the usual care group ( $P < 0.001$ , NNT 286), and colorectal cancer mortality was significantly reduced with sigmoidoscopy compared to usual care (0.33% vs 0.44%, respectively,  $P < 0.001$ , NNT 870) (level 1 [likely reliable] evidence). Incidence per 10,000 person-years was 5.6 (sigmoidoscopy) vs 7.9 (usual care) for distal colorectal cancer ( $P < 0.95$ ) and 6 vs 7, respectively, for proximal colorectal cancer. There was no significant difference in death from other causes, excluding prostate, lung, and ovarian cancers (11.8% [sigmoidoscopy] vs 12% [usual care]) [N Engl J Med 2012 Jun 21;366(25):2345].

## ENDOCRINOLOGY

### **Omega-3 Fatty Acid Supplementation Does Not Reduce Mortality or Cardiovascular Events in Patients With or at High Risk of Diabetes**

Evidence for the effect of omega-3 fatty acids on cardiovascular risk has been inconsistent. The Outcome Reduction With an Initial Glargine Intervention (ORIGIN) trial examined the effects of supplementation in 12,611 patients with impaired fasting glucose,

impaired glucose tolerance, or type 2 diabetes. Patients  $>50$  years old (mean age 64 years, 88% with diabetes) were randomized to omega-3 fatty acids 1 g orally once daily (Omacor capsule, sold in United States as Lovaza) vs placebo. All patients had preexisting cardiovascular disease (myocardial infarction, stroke, or revascularization in 59%) or cardiovascular risk factors at baseline. Patients were also randomized to open-label insulin glargine vs standard care. These groups were pooled for the primary analysis of the effects of omega-3 supplementation.

At median follow-up of 6.2 years, there were no significant differences between groups in cardiovascular mortality (9.1% [omega-3] vs 9.3% [placebo]) or all-cause mortality (15.1% vs 15.4%, respectively) (level 1 [likely reliable] evidence). There were also no significant differences in fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, heart failure-related hospitalization, or revascularization procedures. Omega-3 supplementation was associated with significant reduction in triglyceride levels ( $P < 0.001$ ) but had no significant effect on other lipid levels. In subgroup analyses, supplementation had no significant effect on cardiovascular mortality in either the insulin glargine or standard care groups [N Engl J Med 2012 Jul 26;367(4):309].

## INFECTIOUS DISEASE

### **Preexposure Prophylaxis With Tenofovir Reduces Risk of HIV Transmission in Serodiscordant Heterosexual Couples**

The Pre-Exposure Prophylaxis (PrEP) trial evaluated the prophylactic efficacy of the combination drug emtricitabine/tenofovir (Truvada) and of tenofovir alone in Uganda and Kenya among heterosexual couples in which 1 partner had HIV-1 infection. A total of 4,758 couples serodiscordant for HIV-1 infection were randomized to 1 of 3 daily oral regimens for the partner without HIV-1 infection: tenofovir 300 mg/d, combination of tenofovir 300 mg plus emtricitabine 200 mg, or placebo. The partner without infection (male partner in 62% of couples) had monthly HIV-1 testing for up to 36 months, and all patients received risk-reduction counseling, condoms, and prevention information. HIV-1 seroconversion occurred in 22 partners with tenofovir alone, 16 partners with emtricitabine/tenofovir, and 58 partners with placebo. The seroconversion rates per 100 person-years were 0.84 for tenofovir alone ( $P < 0.001$  vs placebo, NNT 73 for 1 year), 0.61 for emtricitabine/tenofovir ( $P < 0.001$  vs placebo, NNT 63 for 1 year), and 2.22 for placebo (level 1 [likely reliable] evidence). The seroconversion rates between the 2 active treatments were not significantly different, and both tenofovir-based regimens were associated with significant reductions in

seroconversion compared to placebo in subgroup analyses of male and female partners. If the seronegative partner was female, the risk reduction was 71% with tenofovir and 66% with combination therapy. For male seronegative participants, the risk reduction was 63% with tenofovir and 84% with combination therapy (N Engl J Med 2012 Jul 11 early online). In July 2012, the Food and Drug Administration approved Truvada for preexposure prophylaxis in persons at high risk of HIV infection and those who engage in sexual activity with partners with HIV infection.

## PEDIATRICS

### **Nebulized Albuterol in Hypertonic Saline Rather than Normal Saline May Reduce Hospitalizations in Young Children With Acute Wheezing**

Virus-induced wheezing is a common cause of emergency department (ED) visits for young children, and symptoms often do not respond to bronchodilators and corticosteroids [N Engl J Med 2009 Jan 22;360(4):339, N Engl J Med 2009 Jan 22;360(4):329]. Previous evidence indicated that nebulized hypertonic saline either alone or mixed with epinephrine may improve outcomes in infants with bronchiolitis [Cochrane Database Syst Rev 2011 Mar 16;(3):CD006458, J Pediatr 2010 Oct;157(4):630]. A small randomized trial evaluated the effects of adding hypertonic saline to albuterol in 41 children aged 1-6 years visiting the ED with acute wheezing episodes. Following a single inhalation of albuterol with normal saline, children were randomized to albuterol mixed with hypertonic saline 5% vs albuterol mixed with normal saline. The study drug was given twice in the ED with 20 minutes between doses and then 4 times daily if the child was admitted to the hospital. Children with viral bronchiolitis were excluded. Albuterol with hypertonic saline was associated with a significant reduction in hospital admission compared to albuterol plus normal saline (62.2% vs 92%, respectively,  $P < 0.05$ , NNT 4). The median hospital stay was 2 days with hypertonic saline vs 3 days with normal saline ( $P = 0.027$ ). Clinical severity scores were significantly reduced in both groups compared to baseline, with no significant differences between groups [Pediatrics 2012 Jun;129(6):e1397] (level 2 [mid-level] evidence).

## PULMONARY MEDICINE

### **Pulse Oximetry Algorithm for Preflight Evaluation May Identify Patients With COPD Who Can Fly Without Further Assessment**

Reduced cabin pressure in aircraft can increase the risk of hypoxemia in patients with chronic obstructive pulmonary disease (COPD). The gold standard for preflight risk assessment is the hypoxia-

altitude simulation test (HAST), but the test is mildly invasive, relatively difficult to perform, and not widely available. A recent study validated an algorithm that simplifies the assessment of the need for in-flight supplemental oxygen. A cohort of 100 patients (mean age 65 years) with moderate to very severe COPD who were referred for preflight testing had both HAST evaluation and oxygen saturation ( $SpO_2$ ) measurement by pulse oximetry. According to the algorithm, supplemental oxygen is required if resting  $SpO_2 < 92\%$  or resting  $SpO_2 = 92\%-95\%$  AND exercise  $SpO_2 < 84\%$ . Supplemental oxygen would not be required if resting  $SpO_2 > 95\%$  AND exercise  $SpO_2 \geq 84\%$ . For patients with other results, the algorithm recommends HAST assessment.

The algorithm was validated in an independent cohort of 50 similar patients. All 16 patients classified as not needing supplemental oxygen were correctly identified (confirmed by HAST). Four patients were incorrectly classified as needing oxygen. Under the British Thoracic Society guideline recommending HAST for any patient with resting  $SpO_2 < 95\%$  at sea level, 27 patients would have required HAST evaluation, but the algorithm indicated HAST for only 20 patients, a reduction of 26% (level 2 [mid-level] evidence). For predicting the need for in-flight supplemental oxygen, the algorithm had 100% sensitivity and 80% specificity (Thorax 2012 Jul 6 early online). One caveat is that pulse oximetry may not accurately reflect arterial oxygenation in certain patients, such as those with hemoglobinopathies.

## RADIOLOGY

### **Childhood CT Scans May Slightly Increase Lifetime Risk of Leukemia and Brain Tumors**

A retrospective study of patients in Great Britain who had at least 1 computed tomography (CT) scan before the age of 22 and no previous cancer diagnosis were evaluated for the risks of leukemia and brain tumors associated with childhood CT scans. A cohort of 178,604 patients was analyzed for incidence of leukemia, and a cohort of 176,587 patients was analyzed for brain tumors. During follow-up of up to 23 years, leukemia was diagnosed in 74 patients (0.04% of cohort), and brain tumors were diagnosed in 135 patients (0.08% of cohort). Increasing radiation dose was associated with increased cancer risk. For each 1 mGy increase in dose, the excess relative risk for leukemia was 0.036 (95% confidence interval [CI] 0.005-0.12), and the excess relative risk for brain tumor was 0.023 (95% CI 0.01-0.049). Compared to cumulative doses  $< 5$  mGy, a cumulative dose of  $\geq 30$  mGy was associated with an increased risk of leukemia (relative risk 3.18, 95% CI 1.46-6.94) and a cumulative dose of 50-74 mGy was

associated with an increased risk of brain tumor (relative risk 2.82, 95% CI 1.33-6.03). In terms of absolute risk, these results correspond to an estimated 1 additional case of leukemia and 1 additional brain tumor over 10 years per 10,000 children having a head CT scan at  $\leq 10$  years old. Though low, these risks should be considered when weighing the clinical value of a CT scan in a child, especially when other options may exist [Lancet 2012 Aug 4;380(9840):499].

*Note: This abstract does not include a level of evidence because the DynaMed editors classified it as a causes and risk factors study rather than as a treatment study and the editors do not typically add level of evidence grades for causes and risk factors. However, if it were classified as treatment, the study would be identified as level 2 (mid-level) evidence because it is a retrospective cohort study with clinical outcomes.*

## UROLOGY

### Radical Prostatectomy May Not Reduce Mortality in Most Men With Localized Prostate Cancer Compared to Watchful Waiting

The best treatment for men with low-risk prostate cancer remains unclear. At the extremes are radical prostatectomy and watchful waiting, but comparative efficacy studies have been inconclusive to date [Cochrane Database Syst Rev 2010 Nov 10;(11):CD006590]. In the Prostate Cancer Intervention Versus Observation Trial (PIVOT), 731 men ( $\leq 75$  years old, mean age 67 years) with localized prostate cancer detected by prostate-specific antigen (PSA) testing were randomized to radical prostatectomy vs watchful waiting from 1994 to 2002 and followed for up to 15 years (median follow-up 10 years). At baseline, all men had PSA  $< 50$  ng/mL and life expectancy of  $\geq 10$  years. During the trial, 77.2% of the radical prostatectomy group and 79.6% of the watchful waiting group received their allocated treatment. There was no significant difference in all-cause mortality between the 2 groups (47.0% [prostatectomy] vs 49.9% [watchful waiting]) (level 2 [mid-level] evidence) in the overall intention-to-treat analysis, but

prostatectomy was associated with a trend toward reduced prostate cancer-related mortality compared to watchful waiting (5.8% vs 8.4%, respectively,  $P=0.09$ ). In a subgroup analysis of 251 men with PSA  $> 10$  ng/mL at baseline, prostatectomy was associated with significant reductions in both all-cause mortality compared to watchful waiting (48.4% vs 61.6%, respectively,  $P<0.05$ , NNT 8) and prostate cancer-related mortality (5.6% vs 12.8%, respectively,  $P<0.05$ , NNT 14) [N Engl J Med 2012 Jul 19;367(3):203].

## VASCULAR MEDICINE

### Adding Aspirin to Compression Therapy May Hasten Venous Ulcer Healing

Venous ulcers, a common complication of venous insufficiency, are usually treated with compression therapy. A trial with 20 patients in 1994 showed that aspirin helped with ulcer healing, but the evidence was insufficient to recommend aspirin use. A new randomized trial investigated the effects of adding aspirin to compression. Fifty-one patients (mean age 60 years) with ulcers  $> 2$  cm were randomized to aspirin 300 mg/d vs no aspirin. All patients received wound care followed by compression therapy. The mean time to healing was 12 weeks for aspirin and 22 weeks for no aspirin ( $P=0.04$ ) (level 2 [mid-level] evidence). The recurrence rates of 25% for aspirin and 33.3% for no aspirin were not significantly different. The mean time to ulcer recurrence was significantly increased in the aspirin group compared to the no-aspirin group (39 days vs 16.3 days, respectively,  $P=0.007$ ) [Ann Vasc Surg 2012 Jul;26(5):620]. Although this trial was also small, the cost and risks associated with aspirin use are low.

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