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Advancing Evidence-Based Practice

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

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CARDIOLOGY

High-Sensitivity Cardiac Troponin T Measured Twice 1 Hour Apart Can Diagnose and Rule Out MI in Most Patients With Chest Pain

A recent cohort study derived and validated a clinical algorithm for early diagnosis of acute MI using a high-sensitivity troponin T (hs-cTnT) assay in the emergency department. A total of 872 patients (median age 64 years) presenting with chest pain were randomly divided into derivation and validation cohorts (436 patients each). In addition to complete clinical assessment, all patients had hs-cTnT assays at presentation and at 1 hour. A 2-part clinical algorithm was developed in the derivation cohort to diagnose or rule out acute MI using the baseline and 1-hour troponin tests. Acute MI is ruled out if the baseline hs-cTnT level is $<$12 ng/L AND the absolute change in hs-cTnT level within 1 hour is $<$3 ng/L. Acute MI is diagnosed if the baseline hs-cTnT level is $\geq$52 ng/L OR the absolute change in hs-cTnT level within 1 hour is $\geq$5 ng/L. Patients meeting neither set of criteria fall into the observation zone.

The incidence of acute MI in the validation cohort was 17%. The algorithm classified 77% of the group: acute MI was diagnosed in 17% and ruled out in 60%. The remaining 101 patients fell into the observation zone (8 of these patients received final diagnosis of acute MI). For diagnosing acute MI, the algorithm had 97% specificity and 84% positive predictive value. For ruling out MI, it had 100% sensitivity and 100% negative predictive value (level 1 [likely reliable] evidence). In overall analysis of both cohorts, 30-day survival was 99.8% in patients with MI ruled out, 98.6% in patients in the observation zone, and 95.3% in patients with MI ruled in ($P<0.001$ for trend) [Arch Intern Med 2012 Sep 10;172(16):1211].

Antihypertensive Drug Therapy for Less Than 5 Years May Not Reduce Mortality or Cardiovascular Events in Adults With Mild Hypertension

A recent Cochrane review compared antihypertensive drug therapy to placebo or no treatment in patients with mild hypertension (systolic blood pressure 140-159 mmHg or diastolic blood pressure 90-99 mmHg). Data from 8,912 patients from 4 randomized trials with treatment duration of 2-5 years were analyzed. Subgroups of patients with mild hypertension were selected from 3 of the trials (7,900 patients, mean age 52 years). In a fourth trial, subgroup data were not available, but $>$80% of the 1,012 participants had mild hypertension (mean age 38 years). First-line antihypertensive drugs included thiazide or thiazide-like diuretics, beta blockers, or reserpine with additional therapies as needed. Comparing any antihypertensive treatment to controls, there were no significant differences in mortality (risk ratio [RR] 0.85, 95% confidence interval [CI] 0.63-1.15), incidence of coronary heart disease (RR 1.12, 95% CI 0.8-1.57), or total cardiovascular events (RR 0.97, 95% CI 0.72-1.32) (level 2 [mid-level] evidence). Antihypertensive treatment was associated with a trend toward reduced risk of stroke (0.3% with antihypertensives vs 0.7% with control, P=0.078) in an analysis of the largest trial (6,061 patients with mild hypertension). In an analysis of all 17,354 patients in that trial, including those with more severe hypertension, antihypertensive treatment was associated with increased withdrawals for adverse events (11.3% vs 2.3%, $P<0.0001$, number needed to harm [NNH] 11) [Cochrane Database Syst Rev 2012 Aug 15;(8):CD006742].

COLORECTAL SURGERY

Antibiotics May Not Improve Outcomes in Uncomplicated Left-Sided Diverticulitis

Practice parameters from the American Society of Colon and Rectal Surgeons (ASCRS) recommend oral or IV broad-spectrum antibiotics for nonoperative management of acute left-sided diverticulitis [Dis Colon Rectum 2006 Jul;49(7):939-944], and antibiotic treatment has become the standard of care for uncomplicated disease. However, little research has been performed to assess the efficacy of this approach. A recent Cochrane review [Cochrane

Database Syst Rev 2012 Nov 14;(11):CD009092] (level 2 [mid-level] evidence) identified only 1 unblinded trial that compared antibiotics to no antibiotics in patients with uncomplicated left-sided diverticulitis.

Patients (n=623, mean age 57 years) with acute uncomplicated left-sided diverticulitis verified by computed tomography were randomized to treatment with broad-spectrum antibiotics for ≥7 days vs no antibiotics and followed for 1 year [Br J Surg 2012 Apr;99(4):532]. Initial IV treatment was a combination of a second- or third-generation cephalosporin and metronidazole, or carbapenem antibiotics, or piperacillin-tazobactam. IV treatment was followed by oral antibiotics (ciprofloxacin or cefadroxil with metronidazole). There were no significant differences between the groups in any clinical outcomes. Recurrent diverticulitis with hospital readmission occurred in 15.8% with antibiotics vs 16.2% without antibiotics. Complications (including sigmoid perforations or abscesses) occurred in 1% with antibiotics vs 1.9% without, and sigmoid resections were performed in 1.6% vs 2.3%. The median hospital stay was 3 days in each group.

The 2 other trials included in the Cochrane review addressed the comparative efficacy of different antibiotic regimens and found no significant differences in outcomes comparing short-duration IV treatment vs >7 days of IV treatment (1 trial with 44 patients) or comparing cefoxitin vs gentamicin plus clindamycin (1 trial with 51 patients).

GASTROENTEROLOGY

Use of Restrictive Transfusion Threshold May Reduce Mortality Compared to Liberal Threshold in Patients With Upper GI Bleeding

A recent randomized trial compared restrictive vs liberal transfusion protocols in 921 adults with acute upper GI bleeding (49% with peptic ulcer, 21% with esophageal varices). Patients were randomized to have a blood transfusion when their hemoglobin reached <7 g/dL with a target range of 7-9 g/dL (restrictive strategy) or when their hemoglobin reached <9 g/dL with a target range of 9-11 g/dL (liberal strategy). Patients reaching the threshold initially received 1 unit of red blood cells that was followed by a second unit if hemoglobin fell below the target range. Exclusion criteria included exsanguinating bleeding and low risk of rebleeding. A total of 889 patients (96.5%) were included in the analysis. The rates of transfusion were 49% with the restrictive strategy and 85% with the liberal strategy ($P<0.001$). All-cause mortality at 45 days was significantly reduced in the restrictive group (5% vs 9%, $P=0.02$, number needed to treat [NNT] 25) (level 2 [mid-level] evidence). The restrictive threshold was also associated with a lower rate of death due to uncontrolled bleeding (0.7% vs 3.1%, $P=0.01$, NNT 42) and of severe adverse events (12% vs 18%, $P=0.01$, NNT 17) [N Engl J Med 2013 Jan 3;368(1):11].

NEUROLOGY

Subthalamic Neurostimulation May Improve Quality of Life and Motor Function in Early Parkinson Disease

In patients with advanced Parkinson disease, deep brain neurostimulation of the subthalamic nucleus (or globus pallidus) has been associated with reduced motor disability and improved quality of life, but this treatment is commonly delayed until more than a decade into the course of the disease. A recent randomized trial investigated the effects of earlier neurostimulation treatment. A total of 251 patients (mean age 52 years, mean duration of disease 7.5 years) were randomized to subthalamic neurostimulation plus medical therapy vs medical therapy alone for 2 years. All patients had fluctuations or dyskinesia present for ≤3 years and mild to moderate impairment in social and occupational functioning. Best medical therapy was assessed for each patient based on European Federation of Neurological Societies and Movement Disorder Society guidelines. Quality of life was assessed with the 39-item Parkinson Disease Questionnaire (PDQ-39), and motor symptom severity was assessed with Unified Parkinson's Disease Rating Scale part III (UPDRS-III).

Subthalamic neurostimulation was associated with a 26% mean improvement in quality of life scores compared to a 1% worsening with medical therapy alone ($P=0.002$) (level 2 [mid-level] evidence). Mean motor symptom severity scores improved by 30% with

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.

neurostimulation and worsened by 12% with medical therapy alone ($P<0.001$). Neurostimulation was also associated with significant improvements in levodopa-induced motor complications, increased time with good mobility and no dyskinesia, and reduced daily levodopa dose. The primary outcome assessments were unblinded. Secondary blinded assessments (without intention-to-treat analysis) corroborated the primary findings. Serious adverse events occurred in 55% of the neurostimulation group vs 44% of the medical-therapy group. Serious adverse events specifically related to the surgical implantation or the neurostimulation device occurred in 18% of patients [N Engl J Med 2013 Feb 14;368(7):610].

OBESITY MEDICINE

Adults Classified as Overweight May Have Lower Mortality Risk Than Normal Weight Adults

Previous research has suggested that mortality is lowest for persons with a body mass index (BMI) of 22.5-25 kg/m^2 and somewhat higher at the lower extreme of normal as well as at higher levels [Lancet 2009 Mar 28;373(9669):1083]. A recent systematic review of 97 prospective cohort studies assessed all-cause mortality risk in a population of more than 2.88 million persons using standard of weight classifications defined by the World Health Organization (WHO). Normal weight is defined as BMI 18.5-24.9 kg/m^2 and overweight as BMI 25-29.9 kg/m^2. Obesity was stratified to 3 classes: class 1 includes BMI 30-34.9 kg/m^2, class 2 is BMI 35-39.9 kg/m^2, and class 3 is BMI $\geq$40 kg/m^2.

During follow-up ranging from 3-42 years, more than 270,000 deaths occurred. Compared to persons of normal weight, mortality was significantly reduced in persons classified as overweight (hazard ratio 0.94, 95% CI 0.91-0.96) in the analysis of 93 studies. No significant difference in mortality occurred in comparing normal weight to class 1 obesity, but mortality was increased in persons with class 2 or 3 obesity (hazard ratio 1.29, 95% CI 1.18-1.41) in the analysis of 32 studies. In subgroup analyses of persons $\geq$65 years old, being overweight was again associated with reduced mortality compared to normal weight (hazard ratio 0.9, 95% CI 0.86-0.95), and there were no significant differences in mortality comparing normal weight to any obesity category [JAMA 2013 Jan 2;309(1):71]. The reduction in mortality associated with being overweight in the current study may be due, in part, to the wide BMI range considered normal by the WHO classification. Nevertheless, these data suggest that categorizing people as overweight or obese by BMI alone may not provide a valid assessment of health risk.

ONCOLOGY

Continuing Tamoxifen Beyond 5 Years May Reduce Recurrence and Mortality in Women With Estrogen Receptor-Positive Early Breast Cancer

In women with estrogen receptor (ER)-positive early breast cancer, adjuvant tamoxifen treatment for 5 years has been associated with reduced recurrence and breast cancer mortality for up to 15 years compared to either no tamoxifen treatment or treatment for 1-2 years [Lancet 2011 Aug 27;378(9793):771]. The newly published Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial evaluated whether continuing tamoxifen for an additional 5 years would further improve outcomes. Women with early breast cancer who had completed 5 years of tamoxifen treatment (n=12,894) were randomized without blinding to continued tamoxifen (20 mg/d) for a total 10 years vs immediate stopping of tamoxifen treatment. ER status was positive in 53% (6,846 women), negative in 10%, and unknown in 37%. At publication, 91% had completed 10 years follow-up and 77% had completed 15 years follow-up. The adherence rates in the 10-year treatment group were 84% at 7 years and $<$60% at 10 years.

In the prespecified subgroup of ER-positive women, the rates of breast cancer recurrence were 18% with 10-year tamoxifen treatment vs 20.8% with 5-year treatment (P=0.002, NNT 36) (level 2 [mid-level] evidence). Tamoxifen for 10 years was associated with reductions in both breast cancer mortality (9.66% vs 11.6%, P=0.01, NNT 52) and all-cause mortality (18.6% vs 21.1% (P=0.01, NNT 40). The benefits of continued treatment for both recurrence and mortality were significant at $\geq$10 years follow-up, but not at 5-9 years follow-up. Continued tamoxifen treatment was associated with increased risk of endometrial cancer (event rate ratio 1.74, 95% CI 1.3-2.34) and pulmonary embolism (event rate ratio 1.87, 95% CI 1.13-3.07), and decreased risk of ischemic heart disease (event rate ratio 0.76, 95% CI 0.6-0.95). There was no significant difference in the rates of endometrial cancer–related death [Lancet 2012 Dec 4 early online].

PRIMARY CARE

Community-Based Screening Identifies Patients $\geq$75 Years Old With Atrial Fibrillation Suitable for Anticoagulants for Stroke Prevention

Treatment with oral anticoagulants is recommended for patients with atrial fibrillation and high stroke risk. The standard tool for stroke risk assessment is the $CHADS_2$ score that assigns a single point for each of congestive heart failure, hypertension, age $\geq$75

years, and diabetes and 2 points for history of stroke. A score of $\geq$2 is considered high risk. A recent population-based cohort study conducted in Sweden assessed the efficacy of a stepwise screening program to identify patients with high stroke risk who would be suitable for anticoagulant treatment. Invitations to participate were sent to all residents of Halmsted, Sweden aged 75-76 years (1,330 residents). The first step included relevant medical history and a 12-lead electrocardiogram. Participants in sinus rhythm with no history of atrial fibrillation who had a $CHADS_2$ score $\geq$2 were invited to perform self-ECG recording with a handheld device for 2 weeks.

Of the 848 residents who accepted the screening invitation, 9% (75 participants) were identified as candidates for starting oral anticoagulant treatment, including 35 patients with a known history of atrial fibrillation who were not already receiving treatment, 10 who were diagnosed with silent atrial fibrillation on the 12-lead ECG, and 30 who were diagnosed with paroxysmal atrial fibrillation. Of these patients, 57 (76%) began anticoagulant treatment. No treatment outcomes were reported (level 3 [lacking direct] evidence) [Circulation 2013 Jan 23 early online] because looking for a reduction in stroke incidence was beyond the scope of this study. However, the study indicates that significant numbers of patients may be eligible for stroke prophylaxis who are not currently being treated and who can be identified through an outreach program.

VASCULAR MEDICINE

Ramipril Improves Walking Ability in Selected Patients With Stable PAD and Intermittent Claudication

A total of 212 patients (mean age 66 years, 83% men) with stable peripheral arterial disease (PAD) and intermittent claudication were randomized to the angiotensin-converting-enzyme (ACE) inhibitor ramipril 10 mg/d orally vs placebo for 24 weeks. All patients were on a stable drug regimen for at least 6 months prior to randomization (55% taking antiplatelet agents, 55% taking statins, 9.4% taking cilostazol). The list of exclusion criteria was long and included blood pressure $\geq$160/100 mmHg, use of ACE inhibitors or angiotensin receptor blockers within 6 months, and any condition other than PAD that limited walking. Quality of life was assessed using the SF-36. Walking performance was assessed at baseline and at 6 months by a treadmill test (3.2 km/h [2 miles/h] and 12% grade).

At baseline, the mean pain-free walking times were 140 seconds for the ramipril group and 144 seconds for the placebo group. The mean maximum walking times were 234 seconds (ramipril) and 238 seconds (placebo). At 6 months, the pain-free walking time was increased by mean 88 seconds with ramipril vs mean 14 seconds with placebo ($P<0.001$), corresponding to an increased walking distance of 184 meters with ramipril (level 1 [likely reliable] evidence). Maximum walking times were increased by mean 277 seconds vs mean 23 seconds ($P<0.001$). Ramipril was also associated with improvements in patient-reported walking distance, walking speed, and stair climbing ($P<0.001$ for each), and in quality of life on the physical component of the SF-36 ($P=0.02$) [JAMA 2013 Feb 6;309(5):453].

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