WARFARIN IS INEFFECTIVE FOR HF WITHOUT AF

- http://dx.doi.org/10.1056/NEJMoa1202299

INFECTIVE ENDOCARDITIS THAT INVOLVES ICDs

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SUBCLINICAL HYPERTHYROIDISM RAISES RISK FOR MORTALITY AND CARDIAC EVENTS

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Interview with: Douglas Bauer, MD
University of California, San Francisco

TREATMENT OF SUBCLINICAL HYPOTHYROIDISM IS ASSOCIATED WITH FEWER ISCHEMIC CARDIAC EVENTS

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CHRONIC URTICARIA MIGHT BE A HARBINGER OF OTHER AUTOIMMUNE DISEASES

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NEW ULTRALONG-ACTING BASAL INSULIN LOWERS RISK FOR OVERNIGHT HYPOGLYCEMIA

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PEER MENTORS AND FINANCIAL INCENTIVES TO IMPROVE DIABETES CONTROL

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WHY SLEEP PATTERNS MATTER

- http://dx.doi.org/10.1126/scitranslmed.3003200

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COMPARISON OF TWO FORMULAS FOR ESTIMATING GFR

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GENITOURINARY TRAUMA WITH FOLEY CATHETERS

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Side B

TIME TO BROADEN HCV TESTING?

- http://dx.doi.org/10.1093/cid/cis011

Interview with: Phillip Coffin, MD
Department of Public Health
San Francisco, California

PREEXPOSURE PROPHYLAXIS TO PREVENT HIV IN MEN WHO HAVE SEX WITH MEN: AT WHAT COST?

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ANTIDEPRESSANTS FOR PATIENTS WITH PARKINSON DISEASE

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NEW DECISION RULE FOR SYNCPE SAFELY LESSENED HOSPITALIZATIONS

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ARB USE IS NOT ASSOCIATED WITH EXCESS CANCER RISK

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MULTIDISCIPLINARY CARE FOR WOMEN WITH BREAST CANCER

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A NEW MESSAGE ABOUT SKIN CANCER FROM THE USPSTF

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EPIDURAL STEROIDS, ETAERCEPT, OR SALINE INJECTIONS FOR SUBACUTE SCIATICA?

- www.annals.org/content/156/8/551.full

LAPAROSCOPIC VS. OPEN REPAIR OF INGUINAL HERNIA

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ESTIMATING MORTALITY AFTER NONCARDIAC SURGERY

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POSSIBLE NEW APPROACH TO NEONATAL THERAPY FOR CEREBRAL PALSY

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WARFARIN IS INEFFECTIVE FOR HF WITHOUT AF

Chronic anticoagulation in patients with heart failure who do not have atrial fibrillation is controversial. In a study in the May 17 New England Journal of Medicine (http://dx.doi.org/10.1056/nejmoa1202299), researchers compared warfarin with aspirin in 2300 patients without contraindications to anticoagulation. All of the patients were in sinus rhythm and had systolic left ventricular ejection fractions lower than 35%. The patients were randomized to either warfarin (with a target international normalized ratio between 2 and 3.5) or 325 mg/day of aspirin.

At an average follow-up of 3.5 years, the primary endpoint of ischemic stroke, intracerebral hemorrhage, or all-cause death was similar in the two groups. The rates of ischemic stroke were significantly lower with warfarin than with aspirin, but major hemorrhage was twice as common. The warfarin patients were within the target INR range two thirds of the time.

This study showed no net benefit of warfarin among patients in sinus rhythm with systolic heart failure. Until now, the use of anticoagulation in this patient population has presumably depended on the instincts of treating clinicians. Whether clinicians will change their practices based on these results remains to be seen.

INFECTIVE ENDOCARDITIS THAT INVOLVES IMPLANTABLE CARDIAC DEVICES

Infection from implantable cardiac devices can manifest in various ways, including pocket-site infection, bacteremia, and device-related endocarditis that involves leads, cardiac
valves, or both. In a study in the April 25 JAMA (http://dx.doi.org/10.1001/jama.2012.497), researchers used data from a prospective registry to investigate the clinical characteristics and outcomes of hospitalized adult patients who met modified Duke criteria for definite infective endocarditis.

There were nearly 3000 cases of endocarditis between June, 2000, and August, 2006. Of the 180 cases that involved cardiac devices, 90% were associated with permanent pacemakers. Staphylococcal species accounted for 70% of the cases, and healthcare-associated infection accounted for half of the cases. In-hospital mortality was 15% and mortality at a year was 25%. Concomitant valve infection was seen in 40% of the patients and was associated with in-hospital mortality. Although the removal of a device was not associated with lower mortality during the index hospitalization, it was associated with survival at a year.

The mortality rates in this relatively large cohort provide further impetus to develop new interventions for preventing infections associated with cardiac devices. Plus, complete device removal lowers mortality and should be performed in all cases where feasible.

**SUBCLINICAL HYPERTHYROIDISM RAISES RISK FOR MORTALITY AND CARDIAC EVENTS**

There are conflicting data on whether subclinical hyperthyroidism is associated with an elevated incidence of coronary heart disease or atrial fibrillation. (Subclinical hyperthyroidism is defined as a thyrotropin level lower than 0.45 mIU/L, with normal free thyroxine and triiodothyronine.) In a meta-analysis on the website of the Archives of Internal Medicine (http://dx.doi.org/10.1001/archinternmed.2012.402), researchers combined the results of 10 prospective cohort studies with more than 50,000 patients with a median age of 59, of whom 2200 had subclinical hyperthyroidism.

During a median follow-up of 9 years, in analyses adjusted for age and sex, the risk for those with subclinical hyperthyroidism compared to those who were euthyroid was increased 25% for overall mortality, 30% for mortality associated with coronary heart disease and 70% for incident atrial fibrillation. The risks were even higher in those with thyrotropin levels lower than 0.1 mIU/L, and the risks did not change after adjusting for other cardiovascular risk factors. The risk attributable to subclinical hyperthyroidism, after accounting for traditional risk factors, was 15% for total mortality and 40% for incident atrial fibrillation.

A guideline (http://dx.doi.org/10.1089/thy.2010.0417) published last year recommends treating subclinical hyperthyroidism to prevent cardiac events and osteoporosis, particularly when thyrotropin levels are lower than 0.1 mIU/L. An editorialist agrees (http://dx.doi.org/10.1001/archinternmed.2012.1114) with these recommendations, particularly for elderly patients with cardiac risks and for patients with osteoporosis, but no large randomized trials have evaluated whether treatment results in actual clinical benefit.

**TREATMENT OF SUBCLINICAL HYPOTHYROIDISM IS ASSOCIATED WITH FEWER ISCHEMIC CARDIAC EVENTS**

Subclinical hypothyroidism (defined as a serum thyrotropin level greater than 5 and up to 10 mIU/L, with a normal free thyroxine level) has been associated with an elevated risk for adverse cardiac events and mortality in middle-aged, but not older, patients. Randomized trials of treating patients with subclinical hypothyroidism have been small and short term, and they have focused on subjective symptoms, not cardiac endpoints.

In a retrospective cohort study on the website of the Archives of Internal Medicine (http://viajwat.ch/JQoaWF), researchers in the United Kingdom identified 3000 younger patients (between the ages of 40 and 70) and nearly 2000 patients older than 70 with subclinical hypothyroidism; roughly half of the patients in each group were treated with levothyroxine (the median dose was 75 µg/day). In analyses adjusted for baseline cardiovascular risk, the number of ischemic heart disease events in the younger patients was 40% lower in those who were treated than in those who were not, during a median follow-up of nearly 8 years. There was no difference between the treated and the untreated older patients.

Because of its retrospective design, this study of patients with subclinical hypothyroidism cannot account for the many possible reasons that some patients were treated and others were not. So, no treatment recommendation can really be made based on these results. The researchers believe that a randomized controlled trial, focused on cardiac outcomes, is justified, but a study that’s adequately powered to show whether treatment improves cardiovascular outcomes or mortality would be very large and long term.

**CHRONIC URTICARIA MIGHT BE A HARBINGER OF OTHER AUTOIMMUNE DISEASES**

Chronic idiopathic urticaria is defined by the presence of hives three or more times/week for at least 6 weeks, with no identifiable trigger. Half of the patients who experience chronic urticaria exhibit IgE autoantibodies or antibodies against high-affinity IgE receptors on mast cells and basophils; experts think that these antibodies are pathogenic.

In a study in the May Journal of Allergy and Clinical Immunology (http://dx.doi.org/10.1016/j.jaci.2012.01.043), researchers in Israel conducted an automated search of a
medicinal database yielding 13,000 patients with chronic idiopathic urticaria; 10% of the patients had hypothyroidism and 3% had hyperthyroidism. Plus, type 1 diabetes, rheumatoid arthritis, celiac disease, lupus, and SJögren syndrome were significantly more common in the patients with chronic urticaria than in a matched control group without urticaria. Not surprisingly, women were at significantly greater risk for developing autoimmune diseases than were men. Of all of the autoimmune diseases that were diagnosed in the urticaria population, more than 80% developed in the 10 years following the diagnoses of chronic urticaria.

These researchers present more evidence that chronic idiopathic urticaria is an autoimmune disease. Patients should be followed closely for the development of other autoimmune disorders, as urticaria typically precedes more serious diseases. But routine laboratory testing for autoimmune markers is not warranted, unless patients have accompanying signs or symptoms that suggest these diseases. Other autoimmune diseases might not present for as long as 10 years, and, as of yet, we do not have a way to prevent disease onset in at-risk patients with abnormal serological markers. Plus, researchers have recently shown that lab testing does not improve the control of chronic urticaria and does not change patient management (http://jwat.ch/JwDiaR).

NEW ULTRALONG-ACTING BASAL INSULIN LOWERS RISK FOR OVERNIGHT HYPOGLYCEMIA

The fear of hypoglycemia, clearly a potentially serious adverse effect of insulin treatment in type 1 and advanced type 2 diabetes, can deter aggressive glycemic control. Some nocturnal hypoglycemia could be related to fluctuating levels of current basal insulins. Insulin degludec is a new ultralong-acting insulin that has not yet been approved by the Food and Drug Administration; its half-life is longer than 25 hours, which is double that of insulin glargine (trade name: Lantus). In the April 21 *Lancet*, researchers present the results from two 1-year randomized noninferiority trials — that involved 630 patients with type 1 diabetes (http://viajwat.ch/K2ITUD) and 740 patients with advanced type 2 diabetes (http://viajwat.ch/KKjvyO) — in which insulin degludec was compared with insulin glargine in basal-bolus insulin regimens. In both of the trials, a treat-to-target design was used to minimize the differences in efficacy between the groups and focus on safety outcomes, including hypoglycemia.

Daily doses of insulin degludec or insulin glargine were titrated to fasting plasma glucose levels of 70 mg/dL to 90 mg/dL (although most of the patients did not meet this aggressive target); three or four daily doses of bolus insulin aspart were titrated after the dose of basal insulin was determined. All of the patients had hemoglobin A₁c levels lower than 10% and had been treated with insulin in the past. The patients with type 2 diabetes were allowed to continue pretreatment metformin, pioglitazone (trade name: Actos), or both.

In both of these trials, the average reduction in hemoglobin A₁c levels was virtually identical in the two groups. Nocturnal hypoglycemia was seen significantly less often with insulin degludec than with insulin glargine in both type 1 and type 2 diabetics. In the patients with type 2 diabetes, significantly fewer total hypoglycemic episodes were seen with insulin degludec than with insulin glargine.

In these two trials, almost 90% of hypoglycemic episodes happened during the day, when hypoglycemia is likely to be largely related to meals and insulin boluses. If insulin degludec gains regulatory approval, whether the modest reductions in nocturnal hypoglycemia will be reproducible and clinically important in usual practice remains to be seen.

These studies were industry-sponsored.

**PEER MENTORS AND FINANCIAL INCENTIVES TO IMPROVE DIABETES CONTROL**

Glucose control rates are suboptimal in patients with type 2 diabetes, particularly among black Americans. In a study in the March 20 Annals of Internal Medicine (www.annals.org/content/156/6/i-50.full), researchers at a Veterans Affairs medical center randomized 118 black patients with hemoglobin A₁c levels greater than 8% to usual care, peer mentoring once/week, or financial incentives. The peer mentors, who were matched by race and age to the study patients, were themselves patients who had progressed from poor to good glycemic control. Each mentor got an hour-long training session on motivational interviewing techniques. The patients in the financial-incentive group were offered US$100 if their hemoglobin A₁c levels decreased by 1% and $200 for a 2% decrease.

At baseline, more than 60% of the patients were taking insulin, and the average hemoglobin A₁c level was 9.7%. At 6 months, the peer mentor group showed a significant reduction in average hemoglobin A₁c. The usual-care and financial-incentive groups did not show significant improvement.

In this study, peer mentoring lowered hemoglobin A₁c levels by approximately 1% — that is an effect equal to that produced by most oral hypoglycemic agents. But the researchers do not report whether these results were mediated by lifestyle changes (like weight loss or more exercise) or by more-intense drug treatment (clinicians could prescribe additional medications at their discretion). Financial incentives failed to significantly lower hemoglobin A₁c levels. This trial would benefit from longer follow-up to ensure that the improvements are sustained, and it should be replicated in other populations.
WHY SLEEP PATTERNS MATTER

It has been suggested that people who habitually sleep fewer than 6 hours/night, or whose sleep patterns do not correspond to normal circadian rhythms, have an excess risk for developing obesity and type 2 diabetes. In a study in the April 11 issue of Science Translational Medicine (http://viajwat.ch/KYoieA), researchers sought to confirm and explain this observation.

Their experiment: Twenty people lived in individual quarters in a sleep laboratory for 6 weeks. They had no contact with the outside world (including cues about nighttime and daytime); the timing of meals, caloric intake, and activity levels were experimentally controlled. For the first 3 weeks, 10 hours of darkness (which was considered to be a “sleep opportunity”) happened during what was nighttime in the outside world. For the next 3 weeks, the amount and timing of darkness was experimentally manipulated to be shorter (providing the equivalent of a 5.6-hour “sleep opportunity” per 24 hours, the rest of which consisted of monitored wakefulness); the darkness started 4 hours later each night, until so-called “nighttime” was beginning during what was actually daytime. A 9-day recovery period consisted of 10 hours of nightly sleep that always happened at true nighttime.

Insulin sensitivity, pancreatic insulin secretion, and resting metabolic rates all dropped during sleep disruption, which raised blood glucose levels. These physiological changes reverted to or toward baseline during the recovery period.

This study provides strong evidence to support the epidemiologic observations that sleep that is regularly short or out of phase with day–night cycles (situations typical of shift work) can cause physiological changes that predispose people to type 2 diabetes.

NEW FIBRATE USE AND RISK FOR RENAL INSUFFICIENCY

The new use of fibrates has been associated with an elevated risk for renal insufficiency. In a study in the April 17 Annals of Internal Medicine (www.annals.org/content/156/8/560.full), researchers in Canada looked at this association in 20,000 patients 66 or older with new prescriptions for fenofibrate. The primary outcome at 3 months was hospitalization for an increase in serum creatinine level. Controls were 60,000 older patients with new prescriptions for ezetimibe, which has no known acute renal effects.

Compared with the ezetimibe patients, the fibrate patients had a doubled risk of hospitalization for a rising serum creatinine level (0.4% vs. 0.2%). Among the 1100 patients for whom serial serum creatinine measurements were available, 9% of the fibrate patients and 0.3% of the ezetimibe patients had increases in creatinine of 50% or greater. The patients with underlying chronic renal disease were more likely to need hospitalization for renal insufficiency than were the patients without that history.

Older patients who got new prescriptions for fibrates had an elevated risk for hospitalization for renal insufficiency. Although the absolute risk was small, the risk rose further among the patients with histories of chronic renal disease. Last year, a study found that fibrates are likely being overprescribed (http://jwat.ch/JwEeUN); when fibrates are clearly indicated (for example, to treat severe triglyceridemia), it would be prudent to start them at a low dose in older patients and to closely monitor renal function.

COMPARISON OF TWO FORMULAS FOR ESTIMATING GLOMERULAR FILTRATION RATE

In the United States, the Modification Of Diet In Renal Disease formula is the most common method used for estimating glomerular filtration rate. But a newer method called the Chronic Kidney Disease Epidemiology Collaboration formula is more accurate in selected populations. In a study in the May 9 JAMA (http://dx.doi.org/10.1001/jama.2012.3954), researchers compared how well the two equations predicted renal-related mortality in 45 different cohorts (including more than a million adult patients, many in general-population cohorts).

Glomerular filtration rate was classified into six categories, ranging from less than 15 mL/minute/1.73 m² to 90 or more mL/minute/1.73 m². Compared with the Modification of Diet in Renal Disease method, the Chronic Kidney Disease Epidemiology Collaboration equation reclassified a quarter of the patients into higher (meaning, better) glomerular filtration rate categories and 0.6% into lower categories. During a median follow-up of 7 years, the Chronic Kidney Disease Epidemiology Collaboration method was significantly more accurate than was the Modification Of Diet In Renal Disease equation for predicting total and cardiovascular-related mortality, both overall and in prespecified subgroups (defined by age, sex, race and ethnicity, and the presence of diabetes and hypertension). The Chronic Kidney Disease Epidemiology Collaboration formula was also more accurate in predicting end-stage renal disease, both overall and in men and elders.

The Chronic Kidney Disease Epidemiology Collaboration formula uses the same data elements as the Modification Of Diet In Renal Disease formula, so there is no incremental cost in switching to this method. Its reclassification of many patients into higher glomerular filtration rate categories would result in more efficient clinical management, with less unnecessary testing and treatment in some cases. Editorialists recommend (http://dx.doi.org/10.1001/jama.2012.4623) that the Chronic Kidney
Disease Epidemiology Collaboration method replace the Modification Of Diet In Renal Disease method in routine laboratory use, but also note that new measures of renal function are needed that are not dependent on spot creatinine excretion.

GENITOURINARY TRAUMA WITH FOLEY CATHETERS

The impetus to reduce Foley catheter use in hospitalized patients comes mostly from a desire to prevent catheter-associated urinary infections. But anyone who practices inpatient medicine is familiar with the agitated older man who yanks at his Foley catheter and induces traumatic injury to the bladder or urethra. In a prospective study in the May Journal of Urology (http://dx.doi.org/10.1016/j.juro.2011.12.113), researchers at the Minneapolis Veterans Affairs hospital collected data on all hospitalized patients with Foley catheters during a 16-month period and determined the incidence of Foley-related trauma.

During 6500 patient-days of Foley catheter use, 90 patients suffered 100 instances of catheter-associated genitourinary trauma. Among the adverse events were 11 cases of a “creation of a false passage,” 7 cases of prostatic or intraperitoneal catheter placement, 7 cases of penile trauma or urethral meatal erosion, and 30 cases of gross hematuria. By comparison, there were 116 episodes of urinary infection in this same cohort, but only 20 met criteria for symptomatic infection (as opposed to asymptomatic bacteriuria).

In hospitalized patients with Foley catheters, genitourinary trauma is likely as important a complication as infection. There are other reasons to avoid using Foley catheters whenever possible: They are associated with delirium, and they can immobilize patients who are otherwise ready to ambulate.

TIME TO BROADEN HCV TESTING?

Amazingly, at least half of the patients with hepatitis C in the United States are not aware of their infections, which might remain undiagnosed until cirrhosis or hepatocellular carcinoma develops. Now that treatments for hepatitis C virus infections are somewhat more effective than in the past, should the policy on screening be changed?

In a cost-effectiveness analysis in the May 1 issue of Clinical Infectious Diseases (http://dx.doi.org/10.1093/cid/cis011), researchers incorporated the newest protease inhibitor drugs and evaluated the benefits of broadening the current screening guidelines from the Centers for Disease Control and Prevention (http://viajwat.ch/Mh0Kvo), which call for testing adults with identified risks only (for example, drug use, blood transfusion before 1992, or unexplained liver enzyme abnormalities).

Adding a one-time screening of people in the general American population between the ages of 20 and 70 proved to be cost-effective, with a reduction of liver-related mortality of about 1% for every 15% of the general population screened. The researchers report that targeted screening for those born between 1945 and 1965 improved cost-effectiveness still further. But they emphasize that hepatitis C virus treatment standards (and related costs) are in such rapid flux that their model might need ongoing adjustment.

As treatment for hepatitis C virus infection improves, screening recommendations will inevitably broaden. In the meantime, clinicians who want to expand their own testing habits will find support in these statistics.

PREEXPOSURE PROPHYLAXIS TO PREVENT HIV IN MEN WHO HAVE SEX WITH MEN: AT WHAT COST?

Every year, there are 50,000 new cases of HIV infection in the United States. Of these, more than half are among men who have sex with men. Two years ago, it was shown that among HIV-negative men who have sex with men, daily prophylaxis with antiretroviral therapy lowered the incidence of HIV infection by 50% to 70% (http://jwat.ch/KmTXzG). In a study in the April 17 Annals of Internal Medicine (www.annals.org/content/156/8/541.full), researchers used modeling to see whether preexposure antiretroviral prophylaxis is cost-effective for preventing HIV infection among men who have sex with men.

Starting preexposure prophylaxis in 20% of the men who have sex with men for 20 years would cost US$98 billion in healthcare-related costs and would save $3 billion in prevented HIV care; the cost per quality-adjusted life-year gained would be $170,000. The per-quality-adjusted life-year cost for covering half of the men who have sex with men would be $190,000. Targeting prophylaxis to high-risk men (with an average of 5 partners/year) would lower per-quality-adjusted life-year cost to $50,000.

Clearly, preexposure prophylaxis is too expensive to implement in developing countries. But given the results of this modeling study, targeting high-risk men who have sex with men for prophylaxis brings the cost down to about $50,000 per quality-adjusted life-year, which is generally considered to be the threshold for cost-effectiveness in the United States.

ANTIDEPRESSANTS FOR PATIENTS WITH PARKINSON DISEASE

It has been shown that cognitive-behavioral therapy (http://jwat.ch/JOCRtd) and nortriptyline (http://jwat.ch/lwFSoh4) can be effective for depressed patients with Parkinson dis-
ease. In a multicenter study in the April 17 issue of Neurology (http://viajwat.ch/Kd6sbo), researchers randomized 115 patients with Parkinson disease and major depression, dysthymia, or subsyndromal depression (but not dementia) to paroxetine, extended-release venlafaxine, or placebo. The initial doses were 10 mg of paroxetine or 37.5 mg of venlafaxine, and then the doses were titrated upward with maximum doses of 40 mg of paroxetine and 225 mg of venlafaxine.

Most of the patients had major depression and had never taken antidepressants. At 3 months, all of the groups showed reductions in the Hamilton rating scale for depression; the active treatments were statistically better than placebo, but equivalent to each other. The rates for response (meaning a 50% or greater decrease on the Hamilton scale) and remission were similar among the three groups.

Because of safety concerns with tricyclic antidepressants, the researchers included venlafaxine, which is a dual-acting serotonin–norepinephrine reuptake inhibitor. Unfortunately, the study enrolled only half of its target number of patients; with larger numbers, some secondary-outcome differences might have been significant (http://viajwat.ch/Ilhoky). This study supports the initial use of a selective serotonin reuptake inhibitor for treating depressed patients with Parkinson disease. But if the response is not sufficient, clinicians should consider other options, like nortriptyline or cognitive-behavioral therapy.

NEW DECISION RULE FOR SYNCPE SAFELY LESSENED HOSPITALIZATIONS

Several years ago, researchers developed a clinical decision rule called the Boston Syncope Criteria to identify syncope patients at risk for adverse outcomes. The rule recommends hospital admission for patients with acute coronary syndrome, conduction disease, a worrisome cardiac history (like dysrhythmia or a pacemaker), valvular heart disease, a family history of sudden death, volume depletion, persistent abnormal vital signs in the emergency department, or a primary central nervous system event.

In a prospective single-site study in the March Journal of Emergency Medicine (http://viajwat.ch/IVMjZ1), researchers evaluated the safety of these criteria in 300 patients with syncope who presented to an emergency department before the implementation of the rule (and were therefore managed at the discretion of their doctors) and 300 patients who presented after the implementation of the rule. Disposition decisions were in accordance with the rule in nearly all of the post-implementation cases. The rate of hospital admission decreased from 70% before implementation to 60% afterward. There were no adverse outcomes within a month for the patients who were discharged according to the rule. The rule had a sensitivity of 100% and a specificity of 60% for identifying patients with adverse outcomes.

The Boston Syncope Criteria seem promising for lowering hospital admissions for patients with syncope. The San Francisco Syncope rule also seemed to be highly sensitive initially, but its sensitivity was not adequate in external validation studies (http://jwat.ch/JQS89M). The Boston Syncope Criteria are more comprehensive and might fare better in external validation.

ARB USE IS NOT ASSOCIATED WITH EXCESS CANCER RISK

Angiotensin-converting–enzyme inhibitors are not associated with an elevated risk for cancer. In contrast, cancer risk associated with angiotensin-receptor blockers is not clear: Two years ago, a meta-analysis of randomized trials revealed an elevated risk (http://jwat.ch/IIuIHn), whereas a meta-analysis from last year — of a larger number of trials and individual patient data — did not (http://viajwat.ch/IJvCsO). In a study on the website of the British Medical Journal (http://dx.doi.org/10.1136/bmj.e2697), researchers in the United Kingdom used a large “real-world” database to evaluate the risk for cancer associated with angiotensin-receptor blocker use.

About 400,000 new users of ace inhibitors and angiotensin-receptor blockers were included. During a median follow-up of 4.6 years, more than 20,000 cancers were diagnosed. The overall risk for cancer was similar among the patients exposed to angiotensin-receptor blockers and among those exposed to ace inhibitors only. Exposure to angiotensin-receptor blockers was associated with significantly elevated risks for breast and prostate cancers, but a longer duration of treatment was not associated with an elevated risk. Angiotensin-receptor blocker exposure was associated with a significantly lower risk for lung cancer, but did not affect the risk for colon cancer.

In this study, angiotensin-receptor blocker use was not associated with an elevated overall risk for cancer, compared with ace inhibitor use. Although angiotensin-receptor blockers were associated with elevated risks for breast and prostate cancers, the absolute effects were small, and the researchers could not exclude confounding. These results should be reassuring to clinicians who prescribe, and patients who take, angiotensin-receptor blockers.

MULTIDISCIPLINARY CARE FOR WOMEN WITH BREAST CANCER

Increasingly, care for patients with breast cancer is provided by multidisciplinary teams. Back in 1995, multidisciplinary team care for all patients with breast cancer was introduced in hospitals in greater Glasgow (this was the intervention area), but not in the rest of west Scotland (this was the nonintervention area). This development afforded researchers the opportunity to retrospectively study whether the care provided by these teams improved health outcomes in nearly 14,000 women with invasive breast
cancer. Details appear on the website of the British Medical Journal (http://dx.doi.org/10.1136/bmj.e2718).

From 1990 to 1995, breast cancer–related mortality was 11% higher in the intervention area than in the nonintervention area. From 1996 to the year 2000, after multidisciplinary care was introduced, breast cancer–related mortality was 18% lower in the intervention area than in the nonintervention area. In 1995, all-cause mortality in the women with breast cancer was similar in the two areas but, by 2000, it was 11% lower in the intervention area.

In this study, the introduction of team care was associated with lower breast cancer–related and all-cause mortality in women with breast cancer. These results are not surprising: The teams involved clinicians from various disciplines (like breast cancer surgeons, pathologists, oncologists, radiologists, and nurses), adhered to evidence-based guidelines, held weekly meetings to discuss cases and treatments, and audited the results. So the affected patients got close attention and state-of-the-art care. But this study had important limitations, including its nonrandomized design and the lack of a cost-effectiveness analysis.

A NEW MESSAGE ABOUT SKIN CANCER FROM THE USPSTF

Back in 2003, the United States Preventive Services Task Force found insufficient evidence to determine whether clinician counseling effectively altered patient behavior to lower the risk for skin cancer. For its latest recommendation, the task force reviewed new evidence on this type of counseling. Their current recommendation statement appears on the website of the Annals of Internal Medicine (http://viajwat.ch/Kd8yb9).

The task force recommends that primary care physicians counsel fair-skinned 10- to 24-year-olds about minimizing ultraviolet radiation exposure to lower the risk for skin cancer. The task force found at least fair evidence that this type of counseling improves important health outcomes and that the benefits outweigh the harms. Evidence showed that counseling interventions in the primary care setting or referred from primary care “moderately” increased sun protection behaviors in children, adolescents, and young adults, although the evidence was not adequate for older patients. Successful interventions included appearance-focused materials and peer counseling sessions.

These recommendations on skin cancer prevention follow similar recommendations by other groups. After decades of research that linked the risk for skin cancer with early sun exposure, a united front is emerging: Younger patients and their families need to understand the risks of early sun and indoor tanning exposure and practice risk reduction. Protection for younger children rests with their parents, and the primary care workforce needs to counsel parents about these issues.

EPIDURAL STEROIDS, ETANERCEPT, OR SALINE INJECTIONS FOR SUBACUTE SCIATICA?

We do not have very effective treatments for lumbosacral radiculopathy, and the evidence to support using the most common invasive intervention, namely, epidural steroid injections, has been conflicting. In a double-blind study in the April 17 Annals of Internal Medicine (www.annals.org/content/156/8/551.full), researchers randomized 80 patients with lumbosacral radiculopathy who had not responded to conservative therapy and had corresponding abnormalities on magnetic resonance imaging to two epidural injections (2 weeks apart) of 60 mg of methylprednisolone, 4 mg of etanercept, or saline. Etanercept was studied because experimental evidence suggested that cytokine inhibitors can have favorable effects on injured nerve roots. All of the patients also got bupivacaine. The primary outcome was leg pain, rated on a scale of 0 to 10.

At baseline, the average level of leg pain was about 6. At 1 month, average pain scores declined more in the epidural steroid group than in the etanercept or saline groups, but no comparisons between the groups reached statistical significance. At 3 months, half of the steroid group, and 40% of the patients in either the etanercept or the saline group reported positive outcomes (which were defined as a 50% or greater reduction in pain and no need for further intervention).

This study did not show a significant benefit of epidural injections with steroids or etanercept, relative to saline injections. Although the small sample size could have contributed to the lack of statistical significance at 1 month, that either intervention would have proved to be better than saline injections at 3 months is not likely. These findings support conservative management during the early stages of sciatica.

LAPAROSCOPIC vs. OPEN REPAIR OF INGUINAL HERNIA

The advantages of open vs. laparoscopic repair of inguinal hernia are frequently debated. In a meta-analysis of 30 randomized trials that involved 7200 patients, researchers compared open and laparoscopic approaches for treating unilateral inguinal hernia. Laparoscopic approaches were classified further as transabdominal preperitoneal (the peritoneal cavity is entered) or totally extraperitoneal. Findings appear in the May Annals of Surgery (http://viajwat.ch/JR13uX) and include:

- The risk for hernia recurrence was significantly higher with laparoscopic than with open repair. The totally extraperitoneal procedure largely accounted for the excess recurrence with laparoscopy.
- Perioperative morbidity was also significantly higher with laparoscopic than with open repair. The transab-
dominal preperitoneal procedure largely accounted for the excess perioperative morbidity.

- Laparoscopic repair was significantly less likely than open repair to result in chronic groin pain and numbness.

This report shows some of the tradeoffs between open vs. laparoscopic hernia repair: Open repair is associated with lower rates of hernia recurrence and less perioperative morbidity, but higher rates of chronic groin pain or numbness. Other tradeoffs are not covered in this analysis; for example, laparoscopic (but not open) repair requires general anesthesia, but convalescence is faster after laparoscopic repair. Given how common inguinal hernia is, it is a good idea for primary care clinicians to be familiar with the general outcomes of the two surgical approaches.

ESTIMATING MORTALITY AFTER NONCARDIAC SURGERY

The revised cardiac risk index is widely used to estimate the risk for cardiac complications in patients undergoing noncardiac surgery (http://jwat.ch/KWNmHD), but there is no comparable tool to predict overall postoperative mortality. To create a tool like that, researchers used a database representing several hundred hospitals that was compiled by the American College of Surgeons. Included were 300,000 patients who underwent noncardiac surgery under general or regional anesthesia. Findings appear in the April Annals of Surgery (http://viajwat.ch/JCCfWJ).

To keep the model simple, the researchers selected three variables, namely American Society of Anesthesiologists Physical Status, surgery-specific risk, and emergent vs. nonemergent surgery, and calculated risk points corresponding to each variable’s effect on mortality. See the table detailing the three predictors of noncardiac surgery mortality (http://jwat.ch/IUcuve). Risk prediction was derived from half of the cohort and performed acceptably in the other half. Thirty-day mortality was:

- Less than 0.1% for patients with 0 to 2 points
- 0.2% for 3 points
- 0.5% for 4 points
- 1.5% for 5 points
- 4% for 6 points
- 10% for 7 points

- 25% for 8 points
- 50% for 9 points

The virtues of this model are its relative simplicity and its derivation from a huge database. Its limitations include subjectivity in the assignment of American Society of Anesthesiologists points, and the need to look up which surgical procedures are designated as low, intermediate, and high risk. The researchers believe that their model can be used as a starting point in bedside estimations of perioperative risk; that conclusion is reasonable, although some patients may have unique clinical characteristics that are not captured by the model’s three variables.

POSSIBLE NEW APPROACH TO NEONATAL THERAPY FOR CEREBRAL PALSY

Cerebral palsy, which affects about 3 out of every 1000 children, is characterized by neuroinflammation mediated by activated microglial cells and astrocytes.

In a study in the April 18 issue of Science Translational Medicine (http://viajwat.ch/JeEnHc), researchers used an experimental condition in baby rabbits that histologically and neurologically resembles cerebral palsy in people to test an agent targeted at neuroinflammation; the agent is a nanoparticle (called a dendrimer) fused to \( n \)-acetyl-l-cysteine. The nanoparticle crosses the blood-brain barrier and is taken up selectively by microglial cells and astrocytes. \( N \)-acetyl-l-cysteine has well-documented antioxidant and anti-inflammatory properties. On postnatal day 1, the rabbits with cerebral palsy and healthy rabbits were injected intravenously with the nanoparticle alone, the nanoparticle fused to \( n \)-acetyl-l-cysteine, free \( n \)-acetyl-l-cysteine, or saline. On day 5, the rabbits with cerebral palsy that were treated with the nanoparticle neurologically and histologically nearly normal, with no evidence of adverse effects. This systemically administered therapy prevented the development of a cerebral-palsy–like condition in baby rabbits. Treatment was administered 1 day after birth. In contrast, cerebral palsy in people often is not recognized for 2 or 3 years. So for this approach to help people, some neonatal sign — presumably an index of neuroinflammation — indicating the need for treatment would have to be identified. Also, although no short-term adverse effects were seen, we need longer-term animal studies to identify possible deleterious effects before any trials in people are contemplated.
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1. A study in the May 17 *New England Journal of Medicine* found that, compared to aspirin, warfarin therapy in patients with heart failure but without atrial fibrillation was associated with:
   (A) A significant decrease in all-cause mortality  
   (B) A significant increase in all-cause mortality  
   (C) Reduced risk for ischemic stroke and intracerebral hemorrhage  
   (D) No net benefit

2. In the April 25 *JAMA*, researchers using data from a prospective registry to study characteristics of infective endocarditis involving implantable devices found that:
   (A) 90% of cases involved permanent pacemakers  
   (B) Health care-associated infection accounted for 80% of the cases  
   (C) In-hospital mortality was 6%  
   (D) Removal of the device reduced mortality during the index hospitalization

3. According to findings of a meta-analysis on the website of the *Archives of Internal Medicine*, subclinical hyperthyroidism is associated with increased risk for:
   (A) All-cause mortality  
   (B) Mortality related to coronary heart disease  
   (C) Incident atrial fibrillation  
   (D) All the above

4. In the May *Journal of Allergy and Clinical Immunology*, researchers show that chronic idiopathic urticaria is a harbinger of:
   (A) Cellulitis  
   (B) Autoimmune disease  
   (C) Renal carcinoma  
   (D) Anxiety disorder

5. In the April 17 *Annals of Internal Medicine*, researchers looked at renal outcomes in patients during the first 3 mo after initiation of fibrate therapy. Compared to patients with new prescriptions for ezetimibe, older patients who were started on fibrates:
   (A) Were at similar risk for hospitalization due to rising levels of serum creatinine  
   (B) Were at slightly lower risk for hospitalization due to rising levels of serum creatinine  
   (C) Had double the risk for hospitalization due to elevated rising of serum creatinine  
   (D) Had no increase in risk for hospitalization for renal insufficiency

6. A prospective study in the May *Journal of Urology* showed that incidence of genitourinary trauma with Foley catheter use is _______ the incidence of catheter-associated urinary tract infections.
   (A) Significantly higher than  
   (B) Significantly lower than  
   (C) Similar to

7. The results of a cost-effectiveness analysis in the May 1 issue of *Clinical Infectious Diseases* support _______ recommendations for screening for hepatitis C infection.
   (A) Broadening  
   (B) Narrowing  
   (C) Maintaining the current

8. On the website of the *British Medical Journal*, researchers looking at cancer rates in patients exposed to angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) found that overall risk for cancer was:
   (A) Significantly greater with ACE inhibitor therapy  
   (B) Significantly greater with ARB therapy  
   (C) Similar in the 2 groups

9. According to a study in the April 17 *Annals of Internal Medicine*, neither etanercept nor epidural methylprednisolone was found to be statistically significantly more effective than saline injections for managing subacute sciatica.
   (A) True  
   (B) False

10. A meta-analysis in the May *Annals of Surgery* compared open and laparoscopic approaches for managing unilateral inguinal hernia. Laparoscopic repair was found to be associated with reduced risk for:
    (A) Recurrence of hernia  
    (B) Perioperative morbidity  
    (C) Chronic groin pain and numbness  
    (D) All the above

Answers to Journal Watch Audio Volume 23, Issue 10: 1-B, 2-C, 3-A, 4-C, 5-A, 6-C, 7-B, 8-B, 9-A, 10-D

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