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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

Participation in Sports Appears Safe for Most Athletes With Implantable Cardioverter Defibrillators

The American College of Cardiology and the European Society of Cardiology recommend that patients with implantable cardioverter defibrillators (ICDs) avoid vigorous sports. In a recent cohort study following 372 athletes with ICDs [Circulation 2013 May 21;127(20):2021], participants who ranged in age from 10 to 60 years old (median age 33 years with ICD for median 27 months) were assessed every 6 months during median follow-up of 31 months. Eighty-eight percent of the participants were active in organized sports (the most common sports were running, basketball, and soccer) that included regular practices and competitions. The others participated in high-risk sports such as skiing or surfing in which injury could result from a loss of control. The most common cardiac diagnoses were long QT syndrome (in 20%) and hypertrophic cardiac myopathy (in 17%), and the most common indications for ICD were ventricular fibrillation or cardiac arrest (in 27%) and syncope (in 27%).

No primary outcome events (defined as serious adverse events during sports or within 2 hours of sports activity) occurred during follow-up. Overall, 21% of participants had at least 1 ICD shock, with appropriate shocks in 13% and inappropriate shocks in 11%. The rate of shocks during activity (in 10% during competition or practice and in 8% during other physical activity) were significantly higher than during rest (6%, $P<0.0001$). Definite lead malfunction occurred in 13 ICDs, with an estimated 5-year malfunction-free survival of 97%, a rate reported to be similar to that in unselected populations. These data may help inform discussions between clinicians and patients with ICDs who wish to participate in sports.

In Patients Taking Oral Anticoagulants Prior to Percutaneous Coronary Intervention (PCI), Addition of Clopidogrel (Alone) Appears as Effective as Clopidogrel Plus Aspirin for Cardiovascular Outcomes and May Reduce Bleeding and Mortality Post-PCI

Antiplatelet therapy is recommended for the prevention of stent thrombosis in patients taking long-term oral anticoagulants who are having percutaneous coronary intervention (PCI), but the combination of antiplatelet and anticoagulant therapies may increase bleeding risks. A recent unblinded randomized trial compared the efficacy of clopidogrel alone vs dual antiplatelet therapy with clopidogrel plus aspirin in 573 patients having PCI [Lancet 2013 Mar 30;381(9872):1107].

Patients (mean age 70 years) were randomized to clopidogrel 75 mg/d vs clopidogrel 75 mg/d plus aspirin 80-100 mg/d (dual therapy). Most patients were taking long-term anticoagulants for atrial fibrillation (69%). All patients started clopidogrel 5 days prior to their PCI with a loading dose of 300 mg at least 24 hours (or 600 mg at least 4 hours) before surgery. Antiplatelet therapy was continued for 1 month to 1 year at the discretion of the treating physician in patients with stable coronary disease who received bare metal stents. Clopidogrel was continued for 1 year in patients with acute coronary syndrome or who received drug-eluting stents. At 1-year follow-up, researchers found no significant differences in cardiovascular outcomes, including rates of myocardial infarction, stroke, stent thrombosis, and target vessel revascularization (level 2 [mid-level] evidence). Clopidogrel monotherapy was associated with reductions in bleeding events (19.4% vs 44.4%, $P<0.0001$, number needed to treat [NNT] 4), blood transfusions (3.9% vs 9.5%, $P=0.01$, NNT 18), and all-cause mortality (2.5% vs 6.3%, $P=0.027$, NNT 27). Cardiovascular mortality was 1.1% with clopidogrel monotherapy and 2.5% with dual antiplatelet therapy (not significant).

DERMATOLOGY

Antibiotics After Incision and Drainage of Uncomplicated Skin Abscesses Do Not Appear to Increase Clinical Cure Rates

Although evidence since the mid-1980s has indicated that antibiotics do not appear to be

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.

necessary in uncomplicated cases of skin abscess, adjunctive systemic antibiotics are often prescribed. A new systematic review analyzed data from 4 randomized trials that evaluated antibiotic treatment following the drainage of uncomplicated skin abscesses in 589 adults and children [Emerg Med J 2013 May 18; early online].

Two trials used antibiotics potentially active against methicillin-resistant *Staphylococcus aureus* (MRSA) (both used trimethoprim-sulfamethoxazole), and 2 trials used antibiotics active against methicillin-sensitive *Staphylococcus aureus* but not MRSA (cephalexin [Keflex] in 1 trial and cephradine in the other). All trials excluded patients with complicated abscesses. Rates of MRSA infection ranged from 53% to 88%. The primary endpoint was clinical cure at 7 days in 3 of the trials and at 10 days in 1 trial. No significant differences occurred in clinical cure rates (odds ratio 1.17, 95% confidence interval [CI] 0.7-1.95) in an analysis of all trials (level 2 [mid-level] evidence). Based on these results, antibiotics do not seem to have a role in the management of uncomplicated abscesses. *Note: Antibiotics still have a role for patients with complicated abscesses (such as those accompanied by systemic symptoms), for immunocompromised patients, and for abscesses with significant surrounding cellulitis or those in areas that are difficult to drain, such as the hand*.

Briakinumab Appears to Reduce Severity of Psoriasis Better Than Methotrexate in Patients With Moderate or Severe Disease

The American Academy of Dermatology recommends oral methotrexate for severe psoriasis in patients who have responded poorly to other therapies, but its efficacy is limited, it can be poorly tolerated, and it has a long list of contraindications. A recent trial compared the efficacy of briakinumab, an experimental human monoclonal antibody, and methotrexate in 317 patients with moderate or severe psoriasis. Patients were randomized to monthly subcutaneous injections of briakinumab vs oral methotrexate plus folate for 52 weeks. Each group received placebos for the other intervention. The primary outcome was clinically meaningful response (defined as $\geq$75% improvement in score on the Psoriasis Area-and-Severity Index [PASI-75]).

A total of 151 patients (48%) completed the trial. Most of the dropouts in both groups were for lack of efficacy (22 of 48 for briakinumab and 95 of 118 for methotrexate). At 52 weeks, significantly more patients achieved PASI-75 in the briakinumab group than in the methotrexate group (66.2% vs 23.9%, $P<0.001$, NNT 3) (level 2 [mid-level] evidence). Briakinumab was also associated with a greater rate of patients achieving a physician's global assessment of either no apparent disease or minimal disease (63% vs 20.2%, $P<0.001$, NNT 3) and with a greater rate of clinically meaningful improvement in quality of life (56.5% vs 18.4%, $P<0.001$, NNT 3). Rates of serious adverse events (including infections and cancer) were higher in the briakinumab group, but the differences were not statistically significant. The pattern of results was similar at an interim analysis at 24 weeks [N Engl J Med 2011 Oct 27;365(17):1586]. In another recent trial, response rates at 12 weeks were significantly higher with briakinumab than with etanercept or placebo [Br J Dermatol 2011 Sep;165(3):652]. *Note: Briakinumab is not yet available for use*.

ENDOCRINOLOGY

Statins Appear Well Tolerated in Most Patients Who Restart Treatment After Discontinuation for Statin-Related Adverse Events

A recent retrospective cohort study investigated the rates of discontinuing and restarting statins in 107,835 patients who received prescriptions from 2000 to 2008 [Ann Intern Med 2013 Apr 2;158(7):526]. Statin therapy was discontinued at least temporarily in 53% of patients overall, and only 17% experienced statin-related adverse events. Of those who had events, 59% discontinued treatment. The most common events were myalgia and myopathy or other musculoskeletal or connective tissue disorders, pain, and fatigue. A total of 6,579 patients who stopped statins because of a statin-related adverse event then restarted statins, with 41% restarting the same drug that they had discontinued. Ninety-two percent of the patients restarting statins remained on treatment at 1

year after the original event. About one-third of those who restarted their original statin were taking the same or a higher dose at 1 year. Of the patients who discontinued for reasons other than adverse events and then restarted, 98% remained on treatment at 1 year after the original discontinuation. These results suggest that the majority of patients who restart statins may find them tolerable over the long term, even if they have a history of adverse reactions. This information may help clinicians counsel patients regarding the risks and benefits of continued statin therapy.

PAIN MANAGEMENT

OnabotulinumtoxinA Appears to Improve Pain and Sleep in Patients With Chronic Postherpetic Neuralgia

About 10% of patients develop severe chronic neuropathic pain following acute herpes zoster; the frequency is higher in older patients. Postherpetic neuralgia can be difficult to manage, and a recent small randomized trial evaluated the efficacy of onabotulinumtoxinA injections for pain relief in chronic postherpetic neuralgia [Clin J Pain 2013 Jan 30; early online].

Thirty adults with postherpetic neuralgia for at least 3 months (mean duration 104 days) were randomized to onabotulinumtoxinA (100 units in 4 mL normal saline) vs placebo in a single treatment of 40 subcutaneous injections. The injections used 30-gauge needles in a chessboard pattern over the affected areas designated by the patients (thoracic dermatomes in 25 patients, brachial plexus in 4 patients, and sciatic nerve in 1 patient). The minimal distance between injection sites was 1 cm. Pain was rated on a 0-10 visual analog scale, and sleep quality was rated on a 0-15 scale by 5-item questionnaire (higher scores indicated worse outcomes). At 4 weeks, pain reduction of at least 50% was reported in 87% with onabotulinumtoxinA compared to 0% with placebo ($P<0.001$, NNT 2) (level 2 [mid-level] evidence). The median time to 50% pain reduction was 7.4 days, and pain reduction was maintained for a median of 16 weeks. The mean sleep scores at 4 weeks were 4.1 with onabotulinumtoxinA vs 8.5 with placebo ($P<0.001$), and this difference was maintained at 16 weeks. No adverse events were reported.

PULMONARY MEDICINE

Delaying Tracheostomy May Reduce Unnecessary Procedures in Mechanically Ventilated Adults Without Increasing Adverse Outcomes

The TracMan trial was a large multicenter randomized trial that compared early vs late tracheostomy in 909 patients admitted to critical care units in the United Kingdom [JAMA 2013 May 22;309(20):2121]. Adult patients (mean age 64 years) who had been on mechanical ventilation for <4 days and were expected to remain ventilated for at least 7 more days were randomized to 1 of 2 tracheostomy protocols. In the early tracheostomy group, patients had the procedure within 4 days of the start of ventilation. In the late tracheostomy group, the procedure was delayed until at least 10 days and performed only if still clinically indicated. Patients were followed for 2 years.

A total of 91.9% received a tracheostomy in the early group (84.6% at <4 days), while only 44.9% of late group had the procedure ($P<0.05$). No significant differences were found in 30-day mortality (30.8% with early vs 31.5% with late tracheostomy) or 2-year mortality (51% vs 53.7%) (level 2 [mid-level] evidence). The median stay in critical care was 13 days in each group. Tracheostomy-related complications (primarily bleeding requiring intravenous fluids or additional intervention) occurred in 5.5% vs 7.8% in the subgroup of patients who had the procedure (5.1% vs 3.6% overall). The trial was terminated early for futility (at 54% of planned enrollment) without a prespecified stopping rule. These data suggest that a wait-and-see approach may help minimize unnecessary tracheostomies that do not improve clinical outcomes.

Tiotropium May Increase Time to Severe Exacerbation in Patients With Poorly Controlled Asthma

A recent report of 2 identical randomized trials evaluated the efficacy of tiotropium for treating exacerbations in patients with poorly controlled asthma. A total of 912 patients (mean age 53 years) who were taking inhaled glucocorticoids and long-acting beta-2 agonists were randomized to inhaled tiotropium 5 mcg (in 2 puffs) vs placebo by Respimat Soft Mist inhaler once daily for 48 weeks. All patients had an Asthma Control Questionnaire score ≥1.5 (on a 7-point scale) and had had at least 1 exacerbation treated with systemic glucocorticoids within the past year. The primary outcome was time to severe asthma exacerbation (defined as either the initiation of systemic glucocorticoids for ≥3 days or a doubling of systemic glucocorticoid dose for ≥3 days in patients with ongoing or preexisting systemic treatment).

Data from the 2 trials were pooled for analysis. Median time to severe exacerbation was not reached in either the tiotropium or the placebo groups. The time until 25% of the group had a severe exacerbation was 282 days with tiotropium vs 226 days with placebo (hazard ratio 0.79, 95% CI 0.62-1) (level 2 [mid-level] evidence). The tiotropium group had 0.53

severe exacerbations per patient year, compared to 0.66 with placebo (P=0.046). Tiotropium was associated with significant improvements in forced expiratory volume in 1 second, forced vital capacity, and peak expiratory flow in both trials. No significant differences in hospitalizations for asthma or adverse events were found, and no deaths occurred in either group [N Engl J Med 2012 Sep 2; early online]. *Note: Tiotropium delivered via the Respimat Soft Mist inhaler has previously been associated with an increased risk of all-cause and cardiovascular mortality in patients with chronic obstructive pulmonary disease (BMJ 2011 Jun 14;342:d3215). This inhaler is currently available in 55 countries but not in the United States*.

Mepolizumab Decreases Exacerbation Risk in Patients With Severe Eosinophilic Asthma

Recurrent exacerbations are common in a large subgroup of patients with asthma characterized by eosinophilic airway inflammation. This form of asthma is frequently unresponsive to corticosteroid treatment. Mepolizumab (a monoclonal antibody that targets interleukin 5, a protein regulating eosinophil production, maturation, and activation) has previously shown clinical benefits in 2 small randomized trials and a trend toward reduced exacerbations in a larger trial in patients with severe eosinophilic asthma. The recently reported Dose Ranging Efficacy and Safety With Mepolizumab in Severe Asthma (DREAM) trial evaluated the efficacy of mepolizumab in 621 patients from 13 countries—the largest trial to date [Lancet 2012 Aug 18;380(9842):651].

Patients aged 12-74 years were randomized to intravenous mepolizumab at 1 of 3 doses (75 mg vs 250 mg vs 750 mg) vs placebo, with infusions once every 4 weeks for 1 year. All patients had a history of $\geq$2 exacerbations requiring steroids in the previous year and had signs of eosinophilic inflammation. The primary outcome was the incidence of clinically significant exacerbation (defined as a validated episode of worsening asthma symptoms requiring oral corticosteroid treatment for $\geq$3 days, hospital admission, or emergency department visit). Eighty-four percent of the randomized patients completed the trial, and 99% were included in a modified intention-to-treat analysis.

At 1 year, the rate of exacerbations was significantly reduced with each mepolizumab dose compared to placebo (level 1 [likely reliable] evidence). Mean rates of exacerbations per patient per year were 1.24 with mepolizumab 75 mg, 1.46 with mepolizumab 250 mg, 1.15 with mepolizumab 750 mg, and 2.4 with placebo ($P\leq$0.0005 for each comparison). Mepolizumab was also associated with significant reductions in serum eosinophil counts. No significant differences occurred in symptom scores, quality of life, or adverse events. *Note: Mepolizumab has not been approved by the Food and Drug Administration for asthma. It is currently available for compassionate use in patients with hypereosinophilic syndrome*.

RHEUMATOLOGY

Severity of Symptoms and Presence of Effusion May Predict Response to Intraarticular Corticosteroid Injection for Knee Osteoarthritis

A recent systematic review of 11 studies assessing the efficacy of intraarticular steroid injections sought to identify the factors associated with a good response in 624 patients with knee osteoarthritis [Rheumatology (Oxford) 2013 June;52(6):1022]. Response-associated factors were identified primarily through post hoc analyses in the original articles; no metaanalysis could be performed because of differences in outcome measures and criteria for symptom change.

Dichotomous factors predicting a good response in at least 1 study included the presence of effusion, the withdrawal of fluid from the knee, the absence of synovitis, and the use of ultrasound guidance for injection delivery. Increasing efficacy was also associated with increasing severity of radiographic degeneration and increasing severity of pain, stiffness, and loss of function. The duration of symptoms was not associated with the response. Although validating these findings in a prospective study would be ideal, this information may help guide patient selection when intraarticular steroids are considered.

VASCULAR MEDICINE

Adding Aspirin to Compression Therapy May Hasten Venous Ulcer Healing

A small trial with 20 patients in 1994 found that aspirin helped with venous ulcer healing, but no follow-up trials were conducted, and current guidelines conclude that evidence is insufficient to recommend aspirin use for venous ulcers. Now, a second randomized trial has investigated the effects of adding aspirin to compression on healing time and recurrence rates. A total of 51 patients (mean age 60 years) with ulcers $>$2 cm associated with chronic venous insufficiency were randomized to aspirin 300 mg/d vs no aspirin. All patients received wound care—including cleaning, debridement, and hydrocolloid dressings—followed by compression therapy with a 2-layer system providing cushioning and continuous pressure. No topical corticosteroids or antiseptics were used. Patients received antibiotics for infected lesions. Exclusion criteria included diabetes, rheumatoid arthritis, peripheral arterial disease, neurological disease, and contraindications to aspirin.

The mean time to healing was 12 weeks for patients receiving aspirin and 22 weeks for patients not receiving aspirin ($P=0.04$) (level 2 [mid-level] evidence). The recurrence rates of 25% for the aspirin group and 33.3% for the no-aspirin group were not significantly different. The mean time to ulcer recurrence was significantly increased in the aspirin group (39 days vs 16.3 days, $P=0.007$) [Ann Vasc Surg 2012 Mar 19; early online]. Although this trial is also small, the cost and risks associated with aspirin use are low.

Extended Anticoagulation With Apixaban or Dabigatran Reduces Recurrent Venous Thromboembolism and Mortality Without Increasing Major Bleeding

Anticoagulation treatment for patients with venous thromboembolisms (VTEs) is generally recommended for at least 3 months, but the risk of recurrence is high. Extended treatment decreases the risk of recurrence but can increase the risk of major bleeding. Two new trials evaluated the safety and efficacy of extended anticoagulation treatment with either apixaban (AMPLIFY-EXT trial) or dabigatran (RE-SONATE trial) (level 1 [likely reliable] evidence).

In the AMPLIFY-EXT trial [N Engl J Med 2013 Feb 21;368(8):699], 2,486 patients with VTE who had already completed 6-12 months of anticoagulation therapy were randomized to apixaban (2.5 mg vs 5 mg) orally twice daily vs placebo for an additional 12 months. Symptomatic or fatal VTE occurred in 1.7% in each apixaban group (2.5 mg and 5 mg doses) and in 8.8% in the placebo group ($P<0.001$, NNT 14 for each apixaban dose). There were no significant differences in the rates of major bleeding among groups (0.1%-0.2% with apixaban vs 0.5% with placebo). The higher apixaban dose was associated with an increase in clinically relevant nonmajor bleeding compared to placebo (4.2% vs 2.3%, $P<0.05$, number needed to harm [NNH] 52). The difference in the rates of clinically relevant bleeding between the lower dose and the placebo (0.7%) was not significant.

In the RE-SONATE trial [N Engl J Med 2013 Feb 21;368(8):709], 1,353 patients with VTE who had completed 6-18 months of anticoagulation therapy were randomized to dabigatran 150 mg orally twice daily vs placebo for 6 months. Recurrent or fatal VTE occurred in 0.4% of patients with dabigatran vs 5.6% of patients with placebo ($P<0.001$, NNT 20). Clinically relevant bleeding occurred in 5.3% vs 1.8% ($P=0.001$, NNH 28), but there was no significant difference in the rates of major bleeding. The same article reported an additional noninferiority study (RE-MEDY trial) comparing dabigatran to warfarin. The rates of recurrent or fatal VTE were similar for the 2 active drugs, but dabigatran was associated with a reduced risk of clinically relevant bleeding (5.6% vs 10.2%, $P<0.001$, NNT 22) and with a nonsignificant reduction in major bleeding (0.9% vs 1.8%, $P=0.06$).

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