The Ochsner Journal 13:3–7, 2013

Advancing Evidence-Based Practice

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

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CARDIOLOGY

Beta Blocker Use May Not Reduce Mortality, Myocardial Infarction, or Stroke in Patients Without Coronary Artery Disease

A large longitudinal study (median follow-up 44 months) assessed the current efficacy of beta blocker treatment in 3 cohorts: 14,043 patients with prior myocardial infarction (MI), 12,012 patients with coronary artery disease (CAD) but no prior MI, and 18,653 patients with at least 3 cardiovascular risk factors. To compare the effects of beta blocker use versus no use, a propensity score was calculated for each patient characterizing his or her likelihood for receiving beta blockers based on multiple demographic factors, medical history, and use of other medications. About half of the patients in each cohort were included in the propensity-matched analyses. There were no statistically significant differences comparing beta blocker use versus no use in all-cause mortality or cardiovascular mortality in any of the 3 cohorts (level 2 [mid-level] evidence). In patients with risk factors for CAD, beta blocker use was associated with trends toward increased risk of both nonfatal MI (P=0.08) and nonfatal stroke (P=0.06). There were no significant differences in the rates of nonfatal stroke and nonfatal MI in either the prior MI cohort or CAD without prior MI cohort [JAMA 2012 Oct 3;308(13):1340]. This study is limited by the inherent problems of cohort studies and the complexity involved with propensity matching. Although this study raises questions regarding the optimal use of beta blockers in patients with known CAD, it does not seem compelling enough to warrant changes in current recommendations.

American Heart Association guidelines, updated in 2011, call for treatment with beta blockers in patients with MI, acute coronary syndrome, or left ventricular dysfunction for up to 3 years (class I recommendation [should be given]) with a weaker recommendation for longer treatment (class IIa recommendation [reasonable to give]). The 2006 guidelines strongly recommended indefinite beta blocker use in these patients. Under the 2011 guidelines, treatment with beta blockers in patients with other vascular diseases "may be considered" (class IIb) [Circulation 2011 Nov 29;124(22):2458].

Intra-Aortic Balloon Pump Does Not Improve Outcomes in Patients With Acute Myocardial Infarction and Cardiogenic Shock

A report of a trial with 600 patients casts serious doubt on the efficacy of intra-aortic balloon pump (IABP) counterpulsation used for blood pressure support in the treatment of acute MI complicated by cardiogenic shock. Patients with acute MI and cardiogenic shock (median age 70 years) who were expected to have a revascularization procedure were randomized to IABP versus no IABP. In the IABP group, the balloon pump was inserted either before or immediately after the revascularization procedure; both the time of insertion and the choice of revascularization procedure were at the discretion of the investigator. There were no significant differences in any clinical outcomes in the intention-to-treat analysis (level 1 [likely reliable] evidence). Comparing IABP versus no IABP, 30-day mortality was 39.7% vs 41.3%, major bleeding occurred in 3.3% vs 4.4%, and reinfarction occurred in 3% vs 1.4%. There were also no significant differences in the rates of peripheral ischemic complications, stroke, or sepsis [N Engl J Med 2012 Oct 4;367(14):1287].

DERMATOLOGY

Single Application of Topical Ivermectin Is Effective for Eradication of Head Lice

Two recent identical randomized trials suggest that topical ivermectin may be an option for the treatment of head lice when local resistance patterns or safety concerns limit the appropriateness of other agents, such as ermethrin, pyrethrin, or malathion. A total of 289 households were randomized in 2 trials to a single application of topical ivermectin 0.5% vs placebo for each household member $\geq$6 months old with at least 1 live head louse. The youngest member of each household who had at least 3 live head lice was included in the primary analysis (83% were $<$12

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.

years old). An extended analysis included patients in the primary analysis plus any other household member with at least 1 live louse (492 additional household members treated).The treatment was applied as a lotion to dry hair (by patient or caregiver), left on for 10 minutes, and then rinsed with water. No nit combing was performed. Data from the 2 trials were pooled for analysis. Patients were followed for 2 weeks. In the primary analysis, 94.9% in the ivermectin group were lice free after 2 days compared to 31.3% in the placebo group ($P<0.001$, number needed to treat [NNT] 2) (level 1 [likely reliable] evidence). The lice-free rate was also higher with ivermectin at 15 days (73.8% vs 17.6%, $P<0.001$, NNT 2) [N Engl J Med 2012 Nov;367(18):1687].

INFECTIOUS DISEASE

Probiotics Reduce Risk of *Clostridium difficile*-Associated Diarrhea in Patients Taking Antibiotics

Diarrhea is a common side effect of antibiotic treatment. Of particular concern is the specific risk of *Clostridium difficile* infection that may cause not just diarrhea, but also colitis and death. A systematic review of 20 randomized trials evaluated the effects of probiotic prophylaxis specifically on the prevention of *C difficile*-associated diarrhea. A total 3,818 children and adults who were taking antibiotics were randomized to probiotic prophylaxis versus placebo or no treatment. Probiotic species included *Lactobacillus*, *Saccharomyces*, and *Bifidobacterium*, with combinations of species in 7 trials. Probiotic treatment lasted for the duration of antibiotic treatment in 7 trials and for up to 14 days after the end of antibiotics in the remaining trials. The probiotic dose was >10 billion colony-forming units/d in 18 trials. Follow-up ranged from the last day of treatment to 3 months. In the overall analysis, probiotic treatment significantly reduced the incidence of *C difficile*-associated diarrhea compared to control (relative risk [RR] 0.34, 95% confidence interval [CI] 0.24-0.49). The median rate of *C difficile*-associated diarrhea in controls was 5%, giving an NNT of 27-40 for probiotic treatment (level 1 [likely reliable] evidence). Probiotics were also associated with a reduced incidence of *C difficile*-associated diarrhea in children in an analysis of 3 trials with 605 patients (RR 0.4, 95% CI 0.17-0.96, NNT 20-417 with diarrhea in 6% of controls) [Ann Intern Med 2012 Nov 13 early online].

NEPHROLOGY

Ciprofloxacin for 7 Days May Be as Effective as 14 Days for Clinical Cure of Acute Pyelonephritis in Women

A total of 248 women (median age 43 years) with a preliminary diagnosis of acute pyelonephritis (bacteremia was present in 27%) were randomized to receive ciprofloxacin 500 mg orally twice daily for 7 days vs 14 days (92 patients were excluded for ineligibility or protocol violation). The first week of treatment was open label, and the second week was placebo controlled. The primary outcome was clinical cure, defined as complete resolution of symptoms during treatment with no recurrence of symptoms or signs of urinary tract infection during follow-up. The clinical cure rates at 10-14 days were 97% with 7-day treatment and 96% with 14-day treatment (noninferiority established) (level 2 [mid-level] evidence). At 42-63 days, both groups had a clinical cure rate of 93% (noninferiority established). There was no significant difference in overall rates of adverse events, but 7-day treatment was associated with lower incidence of mucosal candida infection after the first week (0% vs 5%, $P=0.036$) [Lancet 2012 Aug 4;380(9840):484].

NEUROLOGY

Dimethyl Fumarate May Decrease Risk of Relapse in Relapsing-Remitting Multiple Sclerosis

Parenteral agents, including interferon and glatiramer, are the most common treatments for relapsing-remitting multiple sclerosis (MS), but adherence can be a concern. The oral drug dimethyl fumarate (BG-12), an antiinflammatory and cytoprotective agent, was submitted for Food and Drug Administration approval for use in relapsing-remitting MS in February 2012. Two recent randomized trials evaluated its efficacy.

In the Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation

(CONFIRM) trial, 1,430 adults with relapsing-remitting MS were randomized to BG-12 240 mg orally (2 times daily vs 3 times daily) vs glatiramer 20 mg subcutaneously daily versus oral placebo for 96 weeks. Both doses of BG-12 were associated with significantly reduced annualized relapse rates compared to placebo. The estimated 2-year risk of relapse was 29% for 2 times daily dosing ($P<0.05$ vs placebo, NNT 9), 24% for 3 times daily dosing ($P<0.05$ vs placebo, NNT 6), and 41% for placebo (level 2 [mid-level] evidence). Glatiramer was also associated with a significantly reduced risk of relapse ($P<0.05$ vs placebo). The most common adverse events with BG-12 were flushing and gastrointestinal symptoms [N Engl J Med 2012 Sep 20;367(12):1087].

In the Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS (DEFINE) trial, 1,237 adults were randomized to the same doses of oral BG-12 as above vs placebo for 96 weeks. As in the CONFIRM trial, both doses of BG-12 were associated with a significant reduction in annualized relapse rates compared to placebo. The estimated 2-year risk of relapse was 29% for 2 times daily dosing ($P<0.05$ vs placebo, NNT 9), 24% for 3 times daily dosing ($P<0.05$ vs placebo, NNT 6), and 41% for placebo (level 2 [mid-level] evidence). Unlike the CONFIRM trial, BG-13 was also associated with reduced risk of disability progression at 2 years, with estimated rates of 16% for 2 times daily dosing ($P<0.05$, NNT 9), 18% for 3 times daily dosing ($P<0.05$, NNT 12), and 27% for placebo [N Engl J Med 2012 Sep 20;367(12):1098].

OBSTETRICS AND GYNECOLOGY

Primary Midwife Care Reduces Cesarean Deliveries in Low-Risk Women

A total of 2,324 women with singleton pregnancy <24 weeks' gestational age were randomized to one-to-one primary midwife care vs usual care through the postpartum period at a single hospital in Melbourne, Australia, in the Comparing Standard Maternity Care With One-to-One Midwifery Support (COSMOS) trial. In the primary midwife care group, a single midwife provided the majority of care for each woman. In the usual care group, women had the option of a midwife team care, care by an obstetric trainee, or combined care by a community-based general practitioner and hospital staff, with care provided by on-duty midwives and doctors for labor, birth, and postnatal care. Most women in the usual care group (78%) received midwife team care. The overall rate of cesarean deliveries was significantly lower with primary midwife care (19.4%) than with usual care (24.9%) ($P=0.001$, NNT 19) (level 1 [likely reliable] evidence). Cesarean rates were also lower in a subgroup analysis of 1,595 primiparous women (24.9% vs 32.4%, $P<0.001$, NNT 14). There were no significant differences in the rate of planned cesarean sections (3.1% vs 3.5%) or in overall cesarean sections in a subgroup of multiparous women (6.2% vs 8%) [BJOG 2012 Nov;119(12):1483]. Several issues may limit the generalizability of these findings: inability to determine if midwife care specifically or continuous care from a single provider is the factor responsible for the results, the difference in cesarean rates around the world and even among institutions in the same area, and the influence of demographic and cultural variables.

ONCOLOGY

Regular Aspirin Use After Diagnosis of Colorectal Cancer May Reduce Mortality in Patients With Tumor PIK3CA Mutation

A total of 964 patients (mean age 68 years, 56% female) with colorectal cancer with known PIK3CA gene status were followed for median 12.75 years. The PIK3CA mutation was present in 16.7%, while the remainder of patients had wild-type PIK3CA cancers. After cancer diagnosis, 41% with the mutation and 42% without the mutation used aspirin regularly (defined as use during most weeks, regardless of dose or indication). Comparing regular aspirin use versus nonuse in patients with the PIK3CA mutation, overall mortality was 27.3% vs 46.3% ($P<0.05$, NNT 6), and cancer-specific mortality was 4.5% vs 27.4% ($P<0.05$, NNT 5) (level 2 [mid-level] evidence). Patients without the mutation had no significant differences in overall mortality (40.7% vs 42.1%) or cancer-specific mortality (19.3% vs 20.6%). About 43% overall used aspirin regularly prior to diagnosis, but there were no significant associations found between prior use and mortality [N Engl J Med 2012 Oct 25;367(17):1596].

ORTHOPEDICS

For Patients With Sciatica, Epidural Corticosteroid Injections May Provide Small Short-Term Benefits for Leg Pain and Disability but No Differences in Outcomes at 1 Year

A recent systematic review compiled data from 23 randomized trials with 2,334 patients who had sciatica for at least 6 weeks to compare epidural corticosteroid injections to placebo. Corticosteroids included methylprednisolone, prednisone, prednisolone, triamcinolone, and betamethasone and were administered by caudal, interlaminar, or transforaminal approaches. Because different scales were used across trials to assess pain and disability, all scores were converted to a 0-100 scale for analysis. The authors considered a reduction of at least 10 points in pain or disability to

be clinically relevant. At follow-up of up to 3 months, epidural steroids were associated with statistically significant reductions in mean leg pain (weighted mean reduction 6.2 points, 95% CI 3-9.4 in analysis of 14 trials with 1,316 patients) and mean disability score (weighted mean reduction 3.1 points, 95% CI 1.2-5 in analysis of 10 trials with 1,154 patients) (level 2 [mid-level] evidence). Neither of these short-term improvements reached the threshold for clinical significance. There were no significant differences in either leg pain or disability at 12 months' follow-up. Low back pain was not significantly reduced in the steroid group at either 3 months' or 12 months' follow-up [Ann Intern Med 2012 Nov 13 early online].

OTOLARYNGOLOGY

Oral Prednisolone Might Not Improve Acute Rhinosinusitis Symptoms

The benefit of corticosteroids in primary care management of sinusitis remains unclear. A recent randomized trial evaluated oral prednisolone in 185 adults with uncomplicated acute rhinosinusitis who visited their primary care physician. Patients (mean age 43 years) with sinusitis symptoms for at least 5 days were randomized to prednisolone 30 mg/d orally versus placebo for 7 days. An analysis of 94% of the randomized patients showed no significant differences in symptom outcomes (level 2 [mid-level] evidence). In the prednisolone group, 62.5% had complete resolution of facial pain or pressure at 7 days compared to 55.8% in the placebo group. The median duration of facial pain was 4.5 days with prednisolone vs 5 days with placebo. The rates of total symptom resolution at 7 days were 32.9% with prednisolone vs 25.3% with placebo. There were no significant differences in health-related quality of life or adverse events at 7 or 14 days or in symptoms at 8-week long-term follow-up [CMAJ 2012 Oct 2;184(14):E751].

PRIMARY CARE

Physicians' Warnings to Unfit Drivers May Reduce Emergency Department Visits for Accidents

A program in which primary care physicians issue warnings to patients judged unfit to drive has been in use in Ontario, Canada, since 1968. A recent cohort study analyzed data from 100,075 consecutive patients who received such warnings since 2006. Patients $\geq$18 years old (57% male) who received warnings (because of medical conditions that included alcoholism, epilepsy, dementia, sleep disorder, fainting or dizziness, stroke, diabetes, and depression without psychosis) were assessed for emergency department visits over 2 time periods: a baseline period consisting of the 3 years prior to the warning and a 1-year follow-up period after the warning. Most of the warnings (98%) were preemptive, coming before the driver experienced a road crash resulting in an emergency room visit. A total of 6,098 physicians participated in the program. Rates of emergency department visits were compared for the baseline and follow-up periods. Visits caused by road crashes in which the patient was a driver were significantly reduced following the warning (4.76 per 1,000 person-years during baseline vs 2.73 per 1,000 person-years during follow-up, $P<0.001$) (level 2 [mid-level] evidence). However, the rate of accident-related visits during follow-up remained higher than the general population rate of 1.98 per 1,000 person-years during the same period (no *P* value reported). The rate of emergency visits for depression increased significantly during follow-up (19.15 vs 23.91 per 1,000 person-years, $P<0.05$), and the warnings may have weakened the patient-doctor relationship. During the follow-up period, the number of return visits to the primary care physician who issued the warning dropped by about 0.66 visits per patient compared to the previous year (no *P* value reported) [N Engl J Med 2012 Sep 27;367(13):1228].

PULMONARY MEDICINE

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

Two identical randomized trials evaluated the efficacy of the anticholinergic agent tiotropium for controlling 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) versus placebo by Respimat Soft Mist inhaler (Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany) once daily for 48 weeks. All patients had an Asthma Control Questionnaire score $\geq$1.5 (on 7-point scale) and 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 $\geq$3 days or a doubling of systemic glucocorticoid dose for $\geq$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 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 were found in hospitalizations for asthma or adverse events, and no deaths occurred in either group [N Engl J Med 2012 Sep 2 early online]. It should be noted that tiotropium delivered via Respimat Soft Mist inhaler has previously been associated with increased risk of all-cause and cardiovascular mortality in patients with chronic obstructive pulmonary disease [BMJ 2011Jun 14;342:d3215]. This inhaler is currently available in 55 countries, but not in the United States.

Acknowledgment

The source of these research summaries is the DynaMed Weekly Update (http://dynamed.ebscohost.com/about/weekly-update), a compilation of articles selected from the top peer-reviewed medical journals as those most likely to change clinical practice. The editor gratefully acknowledges DynaMed's permission to present this material.