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Advancing Evidence-Based Practice

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Most Likely to Change Clinical Practice

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CARDIOLOGY

Walking Appears to Reduce Risk of Cardiovascular Events in Patients With Impaired Glucose Tolerance at Risk of Cardiovascular Disease

Lifestyle modifications have been shown to reduce the rate of progression to type 2 diabetes in patients with impaired glucose tolerance, but the impact of lifestyle changes on cardiovascular outcomes in patients with impaired glucose metabolism has remained unclear. Now, a cohort analysis of data from a randomized trial evaluates the association between walking and the risk of cardiovascular events in a patient population at risk of developing cardiovascular disease.

A total of 9,018 patients with impaired glucose tolerance and increased risk of cardiovascular disease from the NAVIGATOR trial were included in the analysis. All patients had existing cardiovascular disease if $\geq$50 years old or had at least 1 additional cardiovascular risk factor if $\geq$55 years old. Ambulatory activity was assessed using a pedometer at baseline and at 12 months (level 2 [mid-level] evidence).

Overall, 531 patients had a cardiovascular event (defined as a composite of cardiovascular mortality, nonfatal stroke, or myocardial infarction) during 45,211 person-years of follow-up. Each increase in activity by 2,000 steps per day (about 20 minutes of walking at a moderate pace) was associated with a decrease in the risk of cardiovascular events, with a hazard ratio of 0.92 (95% confidence interval [CI] 0.86-0.99) when evaluating the change in activity level from baseline to 12 months. Similarly, a higher baseline activity rate was also associated with decreased risk of cardiovascular events, with a hazard ratio of 0.9 (95% CI 0.84-0.96). These findings were consistent across additional analyses adjusted for all potential confounders evaluated, including treatment group and changes in body mass index [*Lancet* 2013 Dec 19 early online].

An important limitation of this study is the large proportion of patients with missing data (25% at baseline and 45% at 12 months), but this study extends the previous findings by evaluating clinical complications among patients with prediabetes, specifically showing decreased cardiovascular events with increased activity levels and quantifying the relationship between activity and cardiovascular risk in a way that is easy to communicate to patients.

NEPHROLOGY

Warfarin May Increase Risk of Bleeding Without Decreasing Risk of Stroke in Elderly Patients With Atrial Fibrillation Receiving Dialysis

Warfarin is widely used for thromboembolic prophylaxis in patients with atrial fibrillation, including patients with chronic kidney disease. A recent randomized trial showed that adjusted-dose warfarin reduces the risk of ischemic stroke or systemic embolism compared to low-dose warfarin or aspirin in patients with moderate kidney disease [*Clin J Am Soc Nephrol* 2011 Nov;6(11):2599]. However, the role of warfarin in patients with more advanced kidney disease remains unclear. No randomized trials evaluating warfarin for prevention of cardiovascular outcomes in patients receiving dialysis have been conducted, and observational studies in this population have been conflicting. Now, a new cohort study has evaluated the use of warfarin among elderly patients on dialysis who developed atrial fibrillation.

A total of 1,626 patients aged 65 years or older receiving hemodialysis or peritoneal dialysis prior to hospitalization for atrial fibrillation were retrospectively evaluated for an association between warfarin use and risk of bleeding or stroke. Bleeding events included intracerebral, gastrointestinal, or intraocular

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bleeding; hematuria; or bleeding at an unspecified location. Stroke events included ischemic stroke, transient ischemic attack, or a retinal infarct. About 46% of patients received warfarin within 30 days of hospital discharge. Comparing the baseline risks for patients receiving warfarin vs those not receiving warfarin, 84% vs 86% had a high risk of bleeding (HAS-BLED score $\geq$3) and 77% vs 69% had a high risk of stroke ($CHADS_2$ score $\geq$2), but *P* values for these differences were not reported (level 2 [mid-level] evidence).

In an unadjusted analysis, the rate of bleeding was 10.9 per 100 person-years with warfarin vs 7.3 per 100 person-years with no warfarin ($P<0.001$), with no significant difference in the rate of stroke (3.4 per 100 person-years with warfarin vs 2.9 per 100 person-years with no warfarin). The results of a separate analysis adjusted for propensity to receive warfarin (with propensity scores based on multiple clinical and demographic factors including baseline risk) were consistent with those of the unadjusted analysis [*Circulation* 2014 Jan 22 early online].

Based on results from several observational studies, oral anticoagulation in patients with advanced kidney disease has been called into question, and the routine use of oral anticoagulants in patients with chronic kidney disease requiring dialysis is no longer recommended in guidelines from either Kidney Disease: Improving Global Outcomes [*Kidney Int* 2011 Sep;80(6):572] or the Canadian Cardiovascular Society [*Can J Cardiol* 2012 Mar-Apr;28(2):125]. The findings from this latest observational study support these updated guidelines and suggest that warfarin may increase the risk of bleeding with no benefit in primary stroke prevention among patients with atrial fibrillation who require dialysis.

NEUROLOGY

In Adults With Restless Legs Syndrome, Pregabalin Has Greater Efficacy With Less Iatrogenic Worsening of Symptoms Than Higher Doses of Pramipexole

Dopamine agonists such as pramipexole and ropinirole are currently the standard first-line treatment for patients with daily symptoms of restless legs syndrome (RLS) but may result in worsening of symptoms months after treatment, an effect known as augmentation. The anticonvulsant pregabalin showed promise as an alternative treatment for RLS in a small randomized trial [*Neurology* 2010 Jun 8;74(23):1897], and now a large randomized trial has compared pregabalin to placebo and to 2 doses of pramipexole.

A total of 731 adults with moderate to severe RLS symptoms for $\geq$6 months were randomized to 1 of 4 oral treatments for 12 weeks: pregabalin 300 mg/d, pramipexole 0.25 mg/d, pramipexole 0.5 mg/d, or placebo. Patients initially randomized to placebo were rerandomized to active treatment with pregabalin, pramipexole 0.25 mg/d, or pramipexole 0.5 mg/d for an additional 40 weeks. RLS symptoms were assessed with the International RLS Study Group Rating Scale (range 0-40, with higher scores indicating greater symptom severity and the minimal clinically important difference defined as 3 points). At baseline, all patients had an RLS symptom score $\geq$15 points (mean score 22.3 points). The 12-week change in RLS symptom score was the primary analysis and included 696 patients (95% of those randomized) who had at least 1 postbaseline assessment (level 2 [mid-level] evidence).

The mean reduction from baseline in RLS symptom score at 12 weeks was 11.4 points with pregabalin ($P<0.001$ vs placebo), 7.8 points with pramipexole 0.25 mg/d (not significant vs placebo), 10.1 points with pramipexole 0.5 mg/d ($P<0.001$ vs placebo), and 6.9 points with placebo. Pregabalin was associated with lower RLS symptom scores than pramipexole 0.25 mg/d or 0.5 mg/d at 52 weeks ($P<0.001$ for each). The proportion of patients with a clinical global impression of *much improved* or *very much improved* symptoms at 12 weeks was 71.4% with pregabalin ($P<0.001$ vs placebo, number needed to treat [NNT] 4), 51.2% with pramipexole 0.25 mg/d (not significant vs placebo), 62.7% with pramipexole 0.5 mg/d ($P=0.002$ vs placebo, NNT 7), and 46.8% with placebo. The augmentation rates at the end of the trial were 2.1% with pregabalin ($P<0.001$ vs pramipexole 0.5 mg/d, NNT 18, and $P=0.08$ vs pramipexole 0.25 mg/d), 5.3% with pramipexole 0.25 mg/d, and 7.7% with pramipexole 0.5 mg/d [*N Engl J Med* 2014 Feb 13;370(7):621]. This trial shows that pregabalin is at least as effective as pramipexole, with a significantly lower rate of augmentation. However, pregabalin has not been studied extensively in this patient population, and long-term safety and efficacy data are not yet available.

In Adults With Unruptured Brain Arteriovenous Malformation, Interventional Therapy Appears to Worsen Outcomes Compared to Medical Management

The increased use of noninvasive neuroimaging has increased the detection of brain arteriovenous malformations. Patients diagnosed with unruptured or asymptomatic arteriovenous malformations may be managed conservatively or offered interventional therapy—including neurosurgery, embolization, and stereotactic radiotherapy—with the aim of obliterating the origin of the malformation. Interventional therapies

have been used successfully, but little clinical evidence is available to guide the choice of interventional therapy or to demonstrate its superiority over conservative management. A prospective population-based cohort study in Scotland showed that patients receiving interventional therapy for arteriovenous malformation had worse outcomes than those who did not [*Lancet Neurol* 2008 Mar;7(3):223]. A new randomized trial compared the addition of interventional therapy to medical management vs medical management alone.

A total of 226 adults (mean age 45 years) with unruptured brain arteriovenous malformation were randomized to medical management alone vs medical management plus interventional therapy. Patients, clinicians, and investigators were aware of treatment assignment. Medical management consisted of pharmacologic therapy for existing medical disorders (such as seizures or headaches) or any coexisting vascular risk factors (such as diabetes or arterial hypertension), as needed. Patients randomized to interventional therapy additionally received neurosurgery, embolization, or stereotactic radiotherapy, either alone or in combination, at the discretion of the local trial investigator. The goal of the interventional therapy was complete eradication of the arteriovenous malformation. The primary outcome was a composite of symptomatic stroke or death (level 2 [mid-level] evidence).

An independent data and safety monitoring board stopped the trial early because of the superiority of medical management alone based on a prespecified stopping value for the primary outcome. The interim analysis included 223 patients (99% of those randomized) with a median follow-up of 33 months. Symptomatic stroke or death occurred in 10% of those receiving medical management alone vs 31% of those receiving interventional therapy plus medical management ($P<0.05$, NNT 5). The incidence of stroke was 11% with medical management alone vs 39% with interventional therapy plus medical management ($P<0.0001$, NNT 4). In addition, neurologic deficits unrelated to stroke occurred in 0.9% of those treated with medical management alone vs 12% of those treated with interventional therapy plus medical management ($P=0.0008$, NNT 9) [*Lancet* 2014 Feb 15;383(9917):614].

The results of this trial extend previous findings from an observational study and further support the conclusion that current interventional therapies for unruptured arteriovenous malformations do not improve cerebrovascular outcomes. However, arteriovenous malformations are associated with a long natural history, and this trial's median follow-up of 33 months limits the ability to make conclusions about long-term effectiveness. In addition, by not including patients who had received previous interventional therapy for brain arteriovenous malformation, patients with a more aggressive disease course may have been excluded, and this exclusion may therefore limit the generalizability of the findings.

Pimavanserin May Reduce Symptoms of Parkinson Disease Psychosis Without Increasing Risk of Motor Function Impairment

Many patients with Parkinson disease will develop psychosis, but few options are available to manage these symptoms. The recommendation of the American Geriatrics Society Beers Criteria is to avoid all antipsychotics except quetiapine and clozapine in patients with Parkinson disease because of the increased risk of worsening Parkinsonian symptoms. Clinical evidence from large studies showing efficacy for reducing psychosis without increased risk of serious adverse events has been lacking. A recent randomized trial compared the new antipsychotic pimavanserin—a selective serotonin 5-HT2A inverse agonist without dopaminergic, adrenergic, histaminergic, or muscarinic affinity—to placebo in patients with Parkinson disease psychosis.

A total of 199 patients $\geq$40 years old with Parkinson disease psychosis were randomized to pimavanserin 40 mg orally once daily vs placebo for 6 weeks. Psychosis symptoms were assessed using the Parkinson disease-adapted scale for assessment of positive symptoms (SAPS-PD), consisting of a global assessment of hallucinations, a global assessment of delusions, and assessments of 7 individual symptoms of Parkinson disease (total score range 0-45, with higher scores indicating worse symptoms). At baseline, all patients had a mini-mental status examination score of at least 21 points, and the mean SAPS-PD score was 15.9 in the pimavanserin group vs 14.7 in the placebo group (not significant) (level 2 [mid-level] evidence).

About 88% of patients completed the trial, and 93% of patients were included in the efficacy analyses. The mean reduction in SAPS-PD symptom score was 5.79 with pimavanserin vs 2.73 with placebo ($P=0.0014$). A separate study estimated the minimal clinically important difference for the SAPS-PD score to be 2.33 points. Similarly, the proportion of patients with at least a 20% reduction in SAPS-PD symptom score was 63% with pimavanserin vs 47% with placebo ($P=0.0242$, NNT 7). The proportion of patients with a clinical global impression of improvement was 49% with pimavanserin vs 26% with placebo ($P=0.0015$, NNT 5). Serious adverse events occurred in 11% of patients receiving pimavanserin and 4% of those receiving placebo (no

P value reported). No treatment-related motor function impairment was observed in either group [*Lancet* 2014 Feb 8;383(9916):523].

Although pimavanserin demonstrated a significant reduction in psychosis symptoms and was generally well tolerated, the short duration of this trial is an important limitation, and longer follow-up is required for both efficacy and safety analyses. Pimavanserin is not currently available, but a new drug application with the US Food and Drug Administration for use in patients with Parkinson disease is expected later this year.

OBSTETRICS/GYNECOLOGY

Maternal Plasma DNA Screening for Fetal Trisomies 21 and 18 May Reduce the Need for Invasive Follow-up Testing Compared to Standard Aneuploidy Screening

Advances in rapid DNA sequencing and sequence analysis have led to the development of new technologies for prenatal screening, including screening for chromosomal abnormalities such as trisomy 21 (Down syndrome) and trisomy 18 (Edward syndrome). Cell-free DNA testing using massively parallel sequencing of maternal plasma has recently been shown to have high predictive performance for detection of fetal trisomy in study populations involving karyotypes associated with very high risk of aneuploidy. Now, a validation cohort study evaluates the prognostic performance of massively parallel sequencing cell-free DNA testing and standard aneuploidy screening for fetal trisomies in a general obstetric population.

A total of 2,042 adult women (mean age 30 years) with singleton pregnancies of gestational age $\geq$8 weeks had cell-free DNA testing and standard aneuploidy screening for detection of fetal trisomies 21, 18, and 13. Cell-free DNA testing consisted of massively parallel sequencing of maternal plasma cell-free DNA from a 10 mL sample of peripheral venous blood taken during the first, second, or third trimester. Standard aneuploidy screening included assays for first- or second-trimester serum markers either with or without nuchal translucency measurement from fetal ultrasound. The reference standard was newborn physical exam or karyotype analysis in the case of nonlive birth. Overall, 1,914 women were included in the analysis (level 2 [mid-level] evidence).

A total of 5 cases (0.3%) of trisomy 21 and 2 cases (0.1%) of trisomy 18 were identified by reference standard. For detection of trisomy 21, cell-free DNA testing had sensitivity of 100%, specificity of 99.7%, positive predictive value of 45.5%, and negative predictive value of 100%. The corresponding performance measures for standard aneuploidy screening were sensitivity of 100%, specificity of 96.4%, positive predictive value of 4.2%, and negative predictive value of 100%. Similarly, for detection of trisomy 18, cell-free DNA testing had sensitivity of 100%, specificity of 99.8%, positive predictive value of 40%, and negative predictive value of 100%. The corresponding performance measures for standard aneuploidy screening were sensitivity of 100%, specificity of 99.4%, positive predictive value of 8.3%, and negative predictive value of 100%. For both trisomy 21 and trisomy 18, cell-free DNA testing was associated with significantly increased specificity and positive predictive value compared to standard aneuploidy screening [*N Engl J Med* 2014 Feb 27;370(9):799].

The results of this study confirm that a negative result with cell-free DNA testing using massively parallel sequencing of maternal plasma is associated with a greatly reduced risk of fetal trisomy 21 and trisomy 18 in a general obstetric population. The positive predictive values for detecting each fetal trisomy were low for both cell-free DNA testing and standard aneuploidy screening, highlighting the need for more invasive confirmatory testing (such as amniocentesis) for diagnosing these conditions in the case of a positive result. However, cell-free DNA testing was associated with significantly higher sensitivity and positive predictive values for both fetal trisomies, meaning that fewer women would be needlessly discomforted by a false positive result, and fewer would require invasive testing for confirmation.

ORTHOPEDICS

Arthroscopic Partial Meniscectomy Does Not Improve Symptoms of Degenerative Medial Meniscus Tear in Patients Without Knee Osteoarthritis

Arthroscopic surgeries for patients with established knee osteoarthritis are becoming less common because of a lack of clinical evidence supporting their use. However, the implications for patients without clearly established knee osteoarthritis have remained unclear. A recent randomized trial comparing meniscectomy to strengthening exercises in patients presenting with degenerative medial meniscus tear and no clear evidence of osteoarthritis (Kellgren-Lawrence grade 0-1) found no significant between-group differences in function, pain, or patient satisfaction scores. Now, a randomized trial compared arthroscopic partial meniscectomy to sham surgery in patients with medial meniscus tear without knee osteoarthritis.

A total of 146 patients aged 35-65 years with symptomatic degenerative medial meniscus tear without knee osteoarthritis were randomized to arthroscopic partial meniscectomy vs sham surgery

and followed for 12 months. Postoperative care, including walking aids and instructions for graduated exercises, was identical for both groups, and all patients were instructed to take over-the-counter analgesics as required. Symptoms were assessed using the Lysholm and Western Ontario Meniscal Evaluation Tool (WOMET) scores, which both range from 0 to 100, with higher scores indicating less severe symptoms. Knee pain was assessed after exercise using a numeric rating scale with a range of 0 to 10, with higher scores indicating greater pain severity (level 1 [likely reliable] evidence).

Both groups had a significant improvement from baseline in symptom and knee pain scores, but no significant between-group differences were apparent for these outcomes at 12 months. The mean improvement in the Lysholm score was 21.7 points in the arthroscopic partial meniscectomy group vs 23.3 points with sham surgery, with a difference of 11.5 points considered clinically meaningful. Similarly, the mean improvement in the WOMET score was 24.6 points with partial meniscectomy vs 27.1 points with sham surgery, with a difference of 15.5 points considered clinically meaningful. The mean improvement in knee pain was 3.1 points with partial meniscectomy vs 3.3 points with sham surgery, with a difference of 2 points considered clinically meaningful. No significant differences in the rate of subsequent knee surgery, patient-reported satisfaction, patient-reported improvement, or serious adverse events were reported [*N Engl J Med* 2013 Dec 26;369(26):2515].

Recent clinical evidence from randomized trials has consistently shown a lack of efficacy of arthroscopic surgeries for patients with knee osteoarthritis, including patients with meniscus tears. This trial extends those findings to patients with meniscus tears but without established knee osteoarthritis, showing no significant difference in symptom or pain scores between patients receiving arthroscopic partial meniscectomy and those receiving sham surgery.

PSYCHIATRY

Parent-Delivered Cognitive Behavioral Therapy May Improve Anxiety in Children

Cognitive behavioral therapy (CBT) has been shown to be effective for childhood and adolescent anxiety disorders, but access to treatment may be limited. A recent randomized trial evaluated a low-intensity CBT intervention delivered by parents (with guidance from therapists) for children with anxiety disorders in the United Kingdom.

A total of 194 children aged 7-12 years with diagnosed anxiety disorders (generalized anxiety disorder, social phobia, separation anxiety disorder, panic disorder/agoraphobia, and specific phobias) were randomized to 1 of 2 parent-delivered CBT interventions vs waitlist control for 12 weeks. In the full-guidance CBT group, parents received a self-help book and had 4 face-to-face meetings and 4 telephone calls with therapists (1 contact weekly for the first 8 weeks, total therapist time $<$5.5 hours) to provide anxiety education, develop a graded exposure plan, and review progress. Parents in the brief-guidance CBT group received similar training and feedback from therapists but with a total of 4 sessions every other week. Families in the waitlist control group were asked to hold off on any anxiety interventions for 12 weeks (level 2 [mid-level] evidence).

At the end of treatment, rates of recovery from the primary anxiety diagnosis were 50% in the full-guidance CBT group and 25% in the waitlist control group (P=0.013, NNT 4). In the full-guidance group, 34% of children recovered from all anxiety diagnoses compared to 11% of controls (P=0.006, NNT 5). Recovery rates were higher in the brief-guidance group than in controls, but the differences were not statistically significant. Both full and brief guidance were associated with higher rates of *much improved* or *very much improved* status on clinical global impression ratings compared to controls. In a follow-up analysis of 49 children from the full-guidance group at 6 months, 76% no longer met the diagnostic criteria for their primary diagnosis [*Br J Psychiatry* 2013 Dec;203(6):436].

While the lack of a true attention control condition weakens this trial's validity, parent-led CBT may be an effective low-cost first-line approach for treating childhood anxiety disorders before seeking more intensive treatment.

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.

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