AMERICAN ACADEMY OF FAMILY PHYSICIANS

LEARNING LINK

CLINICAL UPDATE

May 28, 2012

JAMA

Sex Differences in Stroke Risk among Older Patients with Recently Diagnosed Atrial Fibrillation

JAMA. May 9, 2012; 307(19): 1952-1958.

A population-based cohort study of patients 65 years or older admitted to the hospital with recently diagnosed atrial fibrillation (AF) included 39 398 men and 44 115 women. Adherence to warfarin treatment was good in both sexes. Crude stroke incidence was 2.02 per 100 person-years in women vs 1.61 per 100 person-years in men ($P < .001$). The sex difference was mainly driven by the population of patients 75 years or older. In multivariable Cox regression analysis, women had a higher risk of stroke than men (adjusted hazard ratio, 1.14; $P < .001$), even after adjusting for baseline comorbid conditions, individual components of the CHADS2 score, and warfarin treatment. **Among older patients admitted with recently diagnosed AF, the risk of stroke was greater in women than in men, regardless of warfarin use. Older women with new onset AF deserve particular attention for stroke prevention.** –dn

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Association between Treatment with Brachytherapy vs. Whole-Breast Irradiation and Subsequent Mastectomy, Complications, and Survival among Older Women with Invasive Breast Cancer

JAMA. May 2, 2012; 307(17): 1736-1745.

A retrospective population-based cohort study of women 67 years or older with incident invasive breast cancer treated with lumpectomy followed by brachytherapy (6952 patients) vs.whole breast radiation (WBI) (85 783 patients) found five-year incidence of subsequent mastectomy was higher in women treated with brachytherapy (3.95% vs WBI 2.18%; $P < .001$) and persisted after multivariate adjustment (hazard ratio [HR], 2.19; $P < .001$). Brachytherapy was associated with more frequent infectious (16.20% vs 10.33%; $P < .001$; adjusted odds ratio [OR], 1.76) and noninfectious (16.25% vs 9.00%; $P < .001$; adjusted OR, 2.03) postoperative complications; and higher 5-year incidence of breast pain (14.55% vs 11.92%), fat necrosis (8.26% vs 4.05%) and rib fracture (4.53% vs 3.62%; $P \leq .01$ for all). Five-year overall survival was 87.66% in patients treated with brachytherapy vs 87.04% in patients treated with WBI (adjusted HR, 0.94; $P = .26$). **In a cohort of older women with breast cancer, treatment with brachytherapy compared with WBI was associated with worse long-term breast preservation and increased complications but no difference in survival.** -dn

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NEJM

Two Year Outcomes after Transcatheter or Surgical Aortic Valve Replacement

NEJM. May 3, 2012; 366:1686-95.

Transcatheter aortic valve replacement (TAVR) is an option for high-risk patients with severe aortic stenosis, but the long-term benefits of this procedure are unknown. In this study, 699 high-risk patients with severe aortic stenosis (defined as an aortic valve area $\leq$ 0.8 cm3 or a mean valve gradient $\geq$ 40 mm Hg) were randomly assigned to either surgical aortic valve replacement or TAVR. Patients were considered high-risk if they had coexisting medical conditions associated with a perioperative mortality risk of at least 15%. Although there were more perioperative deaths in the open surgical group, there was no difference between the two groups in overall mortality at 2 years (33.9% in the TAVR group and 35.0% in the surgery group; P=0.78). There was also no difference in stroke frequency at 2 years (HR, 1.22 for the TAVR group; 95% CI, 0.67 to 2.23; P=0.52). However, paravalvular regurgitation was more frequent with TAVR (P <0.001) and even mild regurgitation was strongly associated with increased "late" mortality. TAVR is an alternative to surgical aortic valve replacement in high-risk patients. The two approaches have different mortality patterns. - CVC

Outcomes of PCI at Hospitals with or without On-Site Cardiac Surgery

NEJM. May 10, 2012; 366:1792-802.

Performance of percutaneous coronary intervention (PCI) is generally limited to hospitals with cardiac surgery back-up. In this study, patients undergoing diagnostic cardiac catheterization at hospitals without cardiac surgery back-up were eligible for the study if the catheterization showed that PCI was indicated. A total of 18 867 patients were randomly assigned in a 3:1 ratio to undergo PCI at that same hospital without surgical back-up (14 149 patients) or at one with on-site cardiac surgery (4 718 patients). There was no difference in the 6-week mortality (0.9% at hospitals without versus 1.0% at hospitals with on-site surgery; P=0.004 for non-inferiority). The rate of major adverse cardiac events at 9 months was 12.1% at hospitals without and 11.2% at hospitals with on-site surgery (P=0.05 for non-inferiority). The rate of target-vessel revascularization was higher in hospitals without on-site surgery (6.5% versus 5.4%; P=0.01). **In this large, multi-site study, PCI performed at hospitals without on-site cardiac surgery was non-inferior to PCI performed at hospitals with cardiac surgery back-up in terms of mortality and major cardiac events.** – CVC

ANNALS OF INTERNAL MEDICINE

Oral Direct Factor Xa Inhibitors versus Low-Molecular Weight Heparin to Prevent Venous Thromboembolism in Patients Undergoing Total Hip or Knee Replacement

Prolonged versus Standard-Duration Venous Thromboprophylaxis in Major Orthopedic Surgery

Ann Int Med. May 15, 2012;156:710-719,720-727.

These two review articles address venous thromboembolism prophylaxis after major orthopedic surgery. The first article is a meta-analysis of 22 trials that compared oral factor Xa inhibitors to low-molecular-weight heparin (LMWH) for thromboprophylaxis in adults undergoing hip or knee replacement. There was no difference in all-cause mortality between groups. Factor Xa inhibitors prevented more symptomatic deep venous thrombosis than LMWH (4 DVT prevented per 1000 treated patients). Increased major bleeding episodes (2 more

events per 1000 treated patients) were seen with factor Xa inhibitors, but only at higher doses. Outcome data was missing for a substantial number of patients and several trials had brief follow up. The authors conclude that, **compared with LMWH, lower doses of oral factor Xa inhibitors reduce symptomatic DVT risk without increasing bleeding**. The second article addressed the question of optimal duration of thromboprophylaxis after major orthopedic surgery. This meta-analysis included 8 RCTs (5 good-quality and 3 fair-quality) to compare prolonged (21 days or longer) with standard (7 to 10 days) thromboprophylaxis. There was high-quality evidence that **prolonged therapy resulted in fewer cases of pulmonary embolism** (OR 0.14; absolute risk reduction [ARR] 0.8%), **asymptomatic DVT** (RR 0.48; ARR 5.8%), **symptomatic DVT** (OR 0.36; ARR 1.5%), **and proximal DVT** (RR 0.29; ARR 7.1%). **Prolonged therapy resulted in more minor bleeding events** (OR 2.44; absolute risk increase 6.3%). - jb

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A Comprehensive Care Management Program to Prevent Chronic Obstructive Pulmonary Disease Hospitalizations

Ann Int Med. May 15, 2012;156:673-683.

This trial attempted to evaluate the efficacy of a comprehensive care management program (CCMP) for reducing COPD hospitalizations. The CCMP entailed 4 individual education sessions and 1 group session, an action plan for COPD exacerbations, and scheduled proactive telephone calls for case management. The trial was stopped after enrollment of 426 patients (44% of planned) due to serious safety concerns. Interim data analysis revealed that the 1-year cumulative incidence of COPD-related hospitalization was 27% with CCMP and 24% with usual care (HR 1.13; p=0.62). More alarmingly, there were **28 all-cause deaths in the intervention group versus 10 deaths in the usual care group** (HR 3.0; p=0.003). An accompanying editorial raises concerns about the institutional review board process. These findings were in sharp contrast to 2 similar prior trials, and evaluating the causes of death did not reveal any pattern or a plausible reason for harm. - jb

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MMWR

Sunburn and Sun Protective Behaviors among Adults Aged 18-29 Years - United States, 2000-2010

MMWR. May 11, 2012; 61(18):317-322.

Sunburn is more common among persons aged 18-29 years compared with older adults. To evaluate trends in sunburn and sun protective behaviors among persons aged 18-29 years, CDC and the National Cancer Institute analyzed data from the 2000, 2003, 2005, 2008, and 2010 National Health Interview Survey (NHIS). The results indicated that although protective behaviors such as sunscreen use, shade use, and wearing long clothing to the ankles have increased in recent years, sunburn prevalence remains high, with 50.1% of all adults and 65.6% of whites aged 18-29 years reporting at least one sunburn in the past 12 months. These results suggest that additional efforts are needed to identify and implement effective strategies targeting younger adults to improve their sun protective behaviors and prevent sunburn and ultimately skin cancer. In 2000, 2005, and 2010, sunburn prevalence was highest among whites (65.6% in 2010) and lowest among blacks (10.9% in 2010). The prevalence of sunburn among men (49.1% in 2010) was not significantly different from the prevalence among women (51.3% in 2010) overall or across racial/ethnic categories. No significant differences in sunburn prevalence were observed in 2010 (50.1% overall) compared with 2000 (50.9% overall). However, sunburn prevalence decreased significantly from 2000 to 2005 (45.5% overall) before increasing in 2010. -jr

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LANCET

(PECEP): an Open-Label Randomized Controlled Trial

Lancet. May 12, 2012;379:1800-1806.

The risk of preterm delivery is significantly increased among women with a short cervix. Previous retrospective studies have shown possible reduction in that risk with the use of pessaries, however no previous randomized, controlled prospective studies have been performed. This multi-center, randomized trial examined whether the use of pessaries would reduce the rate of preterm delivery. 385 pregnant women with ultrasound identified short cervix were assigned to either pessary (n-192) or usual care (n-193). The primary end point was spontaneous delivery prior to 34 weeks gestation. **Pessary use was associated with a significant reduction in preterm delivery (6% (n=12) vs. 27% (n=51), odds ratio 0.18, p<0.0001).** The authors conclude that pessary use may significantly reduce preterm delivery among patients identified with short cervix via 20-23 week ultrasound. –pl

BRITISH MEDICAL JOURNAL

Long Term Outcomes in Men Screened for Abdominal Aortic Aneurysm: Prospective Cohort Study

BMJ. May 19,2012;344:e2958.

Screening men over 65 years of age for abdominal aortic aneurysm has been recommended, and most screening protocols use a threshold aortic diameter of ≥30 mm. This prospective cohort study from Scotland attempted to determine morbidity and mortality in relation to presence of abdominal aortic aneurysm and three categories of aortic diameter (≤24 mm, 25-29 mm, and ≥30 mm). When 8146 men aged 65-74 were screened using ultrasound, 14 men (5.1%) had an aneurysm (diameter ≥30 mm), 669 (8.2%) an aortic diameter of 25-29 mm, and 7063 (86.7%) an aortic diameter of ≤24 mm. The cohort was followed for a median of 7.4 years (interquartile range 6.9-8.2). Mortality was significantly associated with aortic diameter: 512 (7.2%) men in the ≤24 mm group died compared with 69 (10.3%) in the 25-29 mm group and 73 (17.6%) in the ≥30 mm group. The mortality risk in men with an aneurysm or with an aorta measuring 25-29 mm was significantly higher than in men with an aorta of ≤24 mm. The increased mortality risk in the 25-29 mm group, however, was reduced when taking confounders such as smoking and known heart disease into account. After adjustment, compared with men with an aortic diameter of ≤24 mm, the risk of hospital admission for cardiovascular disease and COPD was significantly higher in men with aneurysm and those with aortas measuring 25-29 mm. Men with an aneurysm also had an increased risk of hospital admission for cerebrovascular disease, atherosclerosis, peripheral arterial disease, and respiratory disease. In men with aortas measuring 25-29 mm, the risk of hospital admission with abdominal aortic aneurysm was significantly higher than in men with an aorta of ≤24 mm (adjusted hazard ratio 6.7, 99% confidence interval 3.4 to 13.2) and this increased risk became apparent two years after screening. **Men with**

abdominal aortic aneurysms and those with abdominal aortas measuring 25-29 mm have an increased risk of mortality and hospital admissions compared with men with aorta diameter ≤24 mm. In men with aortic diameter 25-29 mm, risk factors should be evaluated, and rescreening considered. -kel

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The Effectiveness of SPARX, a Computerized Self Help Intervention for Adolescents Seeking Help for Depression: Randomized Controlled Non-Inferiority Trial

BMJ. May 19, 2012;344:e2598.

Up to 25% of young people will experience a depressive disorder by the age of 19. Cognitive behavioral therapy (CBT) is recommended as the preferred treatment for mild to moderate depressive disorders. However, fewer than one fifth of young people with depression receive treatment, partly because of shortage of therapists and economic issues, and partly because young people may be reluctant to seek traditional help. This multicenter randomized controlled non-inferiority trial evaluated whether a new computerized therapy intervention (SPARX, Smart, Positive, Active, Realistic, X-factor thoughts), involving seven modules delivered over four to seven weeks, could reduce depressive symptoms in adolescents seeking help as much or more than CBT delivered by clinical psychologists and counselors. Participants included 187 adolescents aged 12-19 with depressive symptoms, with no major risk of self harm and deemed in need of treatment by their primary health providers: 94 were allocated to SPARX and 93 to treatment as usual. 94 participants were allocated to SPARX (mean age 15.6 years, 62.8% female) and 93 to treatment as usual (mean age 15.6 years, 68.8% female), and were assessed after intervention and at three months. SPARX was not inferior to treatment as usual. Post-intervention, there was a mean reduction of 10.32 in SPARX and 7.59 in treatment as usual in raw scores on the children's depression rating scale-revised (between group difference 2.73, 95% confidence interval −0.31 to 5.77; P=0.079). Remission rates were significantly higher in the SPARX arm (n=31, 43.7%) than in the treatment as usual arm (n=19, 26.4%) (difference 17.3%, 95% confidence interval 1.6% to 31.8%; P=0.030) and response rates did not differ significantly between the SPARX arm (66.2%, n=47) and treatment as usual arm (58.3%, n=42) (difference 7.9%, −7.9% to 24%; P=0.332). **SPARX, a computerized behavioral therapy program aimed at adolescents with depressive disorders, is a potential alternative to traditional therapy for adolescents with depressive symptoms presenting in the primary care setting.** Adolescents also may be more willing and able to participate in a web-based program rather than traditional therapy. -kel

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PEDIATRICS

Effective Analgesia using Physical Interventions for Infant Immunizations

Pediatr. May 2012; 129:815-822.

Many parents and medical providers are concerned about the pain that immunizations cause young infants. Analgesics such as acetaminophen and ibuprofen have been popular adjuncts to childhood vaccines but, over the years, studies have questioned their efficacy and suggest a blunt in immunogenicity. While an oral sucrose solution has been shown to be an effective nonpharmacologic approach to pain relief, Harrington et al evaluated the therapeutic role of Dr. Harvey Karp's 5S's (swaddling, side/stomach position, shushing, swinging and sucking) on post-vaccine comfort during the 2- and 4-month well visits. Using a prospective, placebo-controlled trial, 230 infants were randomized into four groups: a control, a sucrose group, and one of two 5S's groups (with and without sucrose). Immediately after the vaccines were administered, a medical provider (pediatric residents trained in the 5S's technique) attempted one of the interventions over the subsequent 30 seconds. **The**

pain scores and crying time improved the most among the infants who received the 5S's, especially the group who didn't consume the oral sucrose. These finding reaffirm that the "best medicine" in young children is tender loving care. – cap

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Diagnostic Imaging and Negative Appendectomy Rates in Children: Effects of Age and Gender

Pediatr. May 2012; 129:877-884.

Appendicitis can be a diagnostic challenge in children, resulting in unnecessary surgery (i.e., a negative appendectomy rate or NAR), a disease complication (e.g., abscess formation and perforation), and medical cost for hospital observation. While cross-sectional imaging (i.e., ultrasounds and/or abdominal CTs) has been shown to improve an NAR rate, it can put the patient at increased risk for excessive radiation exposure and potentially unnecessary health care costs. Using a retrospective review of a database from 40 US pediatric emergency departments, the authors analyzed the effects of age and gender on these diagnostic imaging tools in altering the NAR. Of the study population, the overall NAR was 3.6%. This rate was found to vary by age and gender and improved when diagnostic imaging was selectively introduced. That is, **cross-sectional imaging reduced NAR (unnecessary surgeries) in all children under the age of 5 years and among girls over the age of 10 years.** A targeted approach in using these radiologic studies should lead to the reduction in unnecessary procedures and costs. – cap

DIABETES CARE

Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach. Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Diabetes Care. April 2012; Published online before print April 19, 2012.

This document published online is a consensus statement from the ADA and EASD. Prior consensus statements have been adopted by the ADA as guidelines, except for the last one which was somewhat of a departure from other expert opinions and guidelines. This document is remarkable in that it is consistent with the very recent AACE/ACE guidelines and ACP guidelines, and thus truly **represents a worldwide consensus on the medical management of hyperglycemia**. Some highlights include the following: glycemic targets and glucose-lowering therapies must be individualized. Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. **Unless there are prevalent contraindications, metformin is the optimal first-line drug. After metformin, there are limited data to guide us**. Combination therapy with an additional 1-2 oral or injectable agents is reasonable, aiming to minimize side effects where possible. In choosing second line agents, the consensus statement recommends **considering hypoglycemia, weight gain, major side effects and cost**. All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. This is a major departure from the last consensus statement the recommended sulfonylureas as the preferred second line therapy. **All agents, including TZD's, DPP4 inhibitors and GLP-1 analogues should be considered when adding diabetes medications.** - mlm

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Glycemic Control over 5 Years in 4,900 People with Type 2 Diabetes: Real-World Diabetes Therapy in a Clinical Trial Cohort

Diabetes Care May 2012; 35(5): 1165–1170.

To assess the adequacy of metformin, sulfonylureas, and insulin to maintain glycemic control and their effects on weight, the investigators observed a cohort of the 4,900 patients for a median of 5 years who were assigned to the placebo arm of The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, as investigators were able to adjust diabetes therapy as they deemed appropriate (real world). Median HbA1c was 6.9% at baseline and increased by an average of 0.22% over 5 years ($P < 0.001$). Median weight was 86.3 kg at baseline and decreased by 0.4 kg over 5 years ($P = 0.002$). Baseline therapy was lifestyle measures only in 27%, oral agents without insulin in 59%, and insulin in 14% (7% also taking oral agents). **Over 5 years, insulin use increased to 32%** (21% also taking oral agents). Use of oral agents remained similar at 56%. **Only 2% of patients at baseline and 4% after 5 years were taking oral agents other than metformin or sulfonylureas**. Initiation of insulin therapy in 855 patients produced a sustained reduction of HbA1c from a median of 8.2 to 7.7%, with a weight gain of 4.6 kg over 5 years. The authors concluded that **with intensification of traditional therapies, glycemic control deteriorated very little over 5 years in a large cohort of type 2 diabetes. However, the requirement for insulin therapy doubled, at the expense of significant weight gain and risk of hypoglycemia**. Whether or not newer agents, i.e. TZD's, DPP4 inhibitors, GLP-1 analogues would prevent the additional requirement is unknown, but other studies suggest this is likely. -mlm

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Eplerenone and Atrial Fibrillation in Mild Systolic Heart Failure

J Am Coll Cardiol, May 1, 2012;59:1598-603.

This study evaluated the incidence of new atrial fibrillation in patients with mild heart failure treated with the aldosterone antagonist eplerenone from the EMPHASIS-HF database. Patients with NYHA functional class II heart failure and with an ejection fraction $\leq$ 35% were enrolled in the study. New onset of atrial fibrillation or flutter (AFF) was reported. The new onset of AFF was significantly reduced in patients treated with eplerenone compared with placebo (2.7% versus 4.5%, hazard ratio 0.58 [0.35-0.96, p=0.034]). The reduction in the primary endpoint of cardiovascular mortality and heart failure hospitalization with eplerenone was similar among patients with and without AFF. **In patients with systolic dysfunction and mild symptoms, the addition of eplerenone reduced the incidence of new onset AFF.** This may lead to long term benefit by preventing heart failure deterioration or complications associated with AFF. - ms

CIRCULATION

Triggers of Hospitalization for Venous Thromboembolism

Circ May 1, 2012;125:2092-2099.

Venous thromboembolism (VTE) hospitalization rates have been increasing. This study evaluated triggers that may lead to hospitalization for VTE. Subjects (n=16 781) were taken from a national sample of older Americans and linked to Medicare files. Outcome was hospitalization for VTE. Exposures during the 90-day

period before hospitalization were compared with exposures in 4 comparison periods. The most common trigger for VTE hospitalization was infection, occurring in 52% of the risk periods before hospitalization. The adjusted incident risk ratio for all infection was 2.90 (2.13-3.94) but a high as 6.92 (4.46-10.72) for infection with a previous hospital or skilled nursing facility stay. Erythropoiesis-stimulating agents and blood transfusions were associated with VTE. Other predictors of VTE included major surgeries, fractures, immobility and chemotherapy. **The new findings of infection, erythropoiesis-stimulating agents, and blood transfusions should be considered when assessing risk for VTE.** - ms