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INSIDE

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Apixaban vs Warfarin for Atrial Fibrillation

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

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Dr. Crawford reports no financial relationships relevant to this field of study. This article originally appeared in the February 2013 issue of Clinical Cardiology Alert.

Synopsis: *The authors concluded that in patients with AF, decreasing GFR was associated with a higher risk of cardiovascular events and bleeding. Apixaban as compared to warfarin reduced these risks regardless of renal function, with the greatest benefit seen in reducing major bleeding in those with impaired renal function.*

Source: Hohnloser S, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: Insights from the ARISTOTLE trial. *Eur Heart J* 2012;33:2821-2830.

Atrial fibrillation (AF) and stroke are common in patients with chronic kidney disease (CKD), but many such patients are not anticoagulated for fear of bleeding complications. In the ARISTOTLE trial of apixaban vs warfarin for stroke prevention in AF, apixaban was associated with a 21% relative risk reduction in stroke, an 11% reduction in total mortality, and a 31% reduction in major bleeding, which were all statistically significant. Since apixaban is 25% eliminated by the kidneys, a secondary analysis of ARISTOTLE based on renal function was pre-specified and is the subject of this report.

There were 7518 patients with an estimated glomerular filtration rate (GFR) > 80 mL/min (42%), 7587 (42%) with a GFR of 50-80, and 3017 (15%) with a GFR < 50. Cystatin C levels also were available in 14,884 patients, permitting a second system for calculating GFR. Comorbidities, estimated stroke risk, and estimated bleeding risk were inversely related to GFR at baseline. Also, the actual incidence of cardiovascular events and bleeding was inversely related to GFR. The annual

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stroke rate was 1.05% in patients with a GFR > 80, 1.46% with a GFR between 50-80, and 2.39% with a GFR < 50. Also, major bleeding increased from 1.65% to 4.8% with decreasing renal function. Apixaban was associated with fewer strokes and less major bleeding regardless of GFR. These results were consistent irrespective of the method of GFR estimation. The relative risk reduction in major bleeding on apixaban was greater in patients with a GFR < 50 (hazard ratio 0.50; 95% confidence interval, 0.38-0.66; $P = 0.005$). The authors concluded that in patients with AF, decreasing GFR was associated with a higher risk of cardiovascular events and bleeding. Apixaban as compared to warfarin reduced these risks regardless of renal function, with the greatest benefit seen in reducing major bleeding in those with impaired renal function.

■ COMMENTARY

Of the new oral anticoagulants, apixaban is the only one to show superiority to warfarin in stroke reduction and safety. This prespecified subgroup analysis of ARISTOTLE represents the largest experience with AF in patients with CKD: more than 10,000 patients. The results were consistent with those of the main trial, despite the fact that a low GFR markedly increased the risk of a vascular event and bleeding complications. The risk of stroke and major bleeding more than doubled at GFRs < 50.

The authors postulate that the higher risk of bleeding on warfarin in CKD patients has diminished enthusiasm for treating these patients with oral anticoagulants. In this study, apixaban was shown to be superior to warfarin, especially in those with GFR < 50. This may change the enthusiasm level for anticoagulation in CKD patients with AF given the higher rate of cardiovascular events in these patients and the availability of a safer agent than warfarin. The study employed half of the usual dose of apixaban in those with a serum creatinine > 1.5 mg/dL, age > 80 years, or weight < 60 kg. Both dabigatran and rivaroxaban have similar dose adjustments for renal compromise, but not for age or weight. Dabigatran and apixaban are dosed twice a day, whereas rivaroxaban has the advantage of once daily dosing. My prediction is now that apixaban has been approved by the FDA, it will be the go-to agent for oral anticoagulation in patients with AF and CKD. ■

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Hepatitis B and C Screening

ABSTRACT & COMMENTARY

By Lin H. Chen, MD

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Dr. Chen has received research grants from the Centers for Disease Control and Prevention and Xcellerex. This article originally appeared in the December 2012 issue of Travel Medicine Advisor.

Synopsis: *Adults with private health care insurance in the United States have suboptimal testing for chronic hepatitis B virus (HBV) and hepatitis C virus (HCV). Clearly, increased awareness is needed regarding HBV and HCV infections, epidemiology, risk, and screening.*

Source: Spradling PR, et al. Hepatitis B and C virus infection among 1.2 million persons with access to care: Factors associated with testing and infection prevalence. *Clin Infect Dis* 2012;55:1047-1055.

This observational cohort study was conducted among 1.25 million adults from four private U.S. healthcare organizations (HCO): Geisinger Health System, Danville, Pennsylvania; Henry Ford Health System, Detroit, Michigan; Kaiser Permanente-Northwest, Portland, Oregon; Kaiser Permanente, Honolulu, Hawaii. The study included persons who had ≥ one clinical encounter during 2006-2008 and ≥ 12 months of follow-up before 2009. The data on infections from this cohort were compared with those from the National Health and Nutrition Examination Survey (NHANES).

Hepatitis B virus (HBV) testing was done on 18.8% of 866,886 persons without a previous diagnosis, resulting in a 1.4% positive rate. Hepatitis C virus (HCV) testing

was done on 12.7% of 865,659 persons without previous diagnosis, resulting in 5.5% positive. Among persons with at least two abnormal serum alanine aminotransferase (ALT), less than half were tested for HBV or HCV. Tests found that Asians were most likely to be infected with HBV (adjusted OR 6.33 compared to whites) whereas persons aged 50-59 years were most likely to be infected with HCV (adjusted OR 6.04 compared to age < 30 years). The investigators estimate from NHANES that nearly one half of HCV and one fifth of HBV infections still remain unidentified.

■ COMMENTARY

It is estimated that 1-2% of the U.S. population has chronic HBV or HCV infection, about 3.5-5.3 million persons, or 3-5 times more frequent than HIV infection. Among them, about 800,000-1.4 million have chronic HBV, while 2.7-3.9 million have chronic HCV.[1] The last few years have brought advances in treatment for both HBV and HCV (for example, tenofovir, entecavir, telaprevir, and boceprevir), and early therapy of chronically infected persons may provide sustained virologic response.

Both HBV and HCV are bloodborne infections. HBV can be transmitted vertically from infected mothers to infants during birth, as well as via sexual contact, sharing needles, and needle stick injuries. Foreign-born persons from endemic countries have an increased likelihood of being chronically infected. Asians and Pacific Islanders are the predominant groups of Americans with chronic HBV infection as well as having a disproportionately high incidence of hepatocellular carcinoma (HCC). However, African-American adults have the highest rate of acute infection, particularly in the South.[1]

HCV is usually transmitted via percutaneous blood exposure, including receipt of a blood transfusion before 1992 when testing for HCV became available, injection drug use, tattooing by unregulated shops, needle sticks, invasive procedures prior to universal precautions, and also sexual contact. African Americans and Hispanics have higher HCV infection rates than whites.[1]

Spradling and colleagues have demonstrated the low testing rates for HBV and HCV among large cohorts in the United States who have private health insurance. Their data substantiate the increased risk for HBV associated with Asian race. They also illustrate the low rate of HBV and HCV testing (14.9%) following determination of an elevated serum ALT, which only increases to 42-44% following a second elevated ALT.

Because more than half of new HBV infections diagnosed in the United States were in foreign-born persons, the Centers for Disease Control and Prevention (CDC) expanded testing recommendations for HBV infection in 2008 to include persons born in countries with HBsAg prevalence of ≥ 2%. Despite this recommendation, and despite the demonstration of cost-effectiveness using 2% prevalence for screening chronic HBV, testing for HBV in the foreign-born has remained inconsistent. Many health care providers still lack knowledge about HBV infection, available tests, screening, and vaccination in these high-risk populations. The Boston Area Travel Medicine Network (BATMN), a research collaboration of five travel clinics in the greater Boston Area, found that only 25% of persons born in countries with HBV prevalence of ≥ 2% had been tested before their pre-travel consultations. An additional 11% of the at-risk travelers tested at the travel clinic visits led to new diagnosis of chronic HBV infection in 3.3%.[9]

Similarly, the CDC has recommended HCV testing for persons with possible exposures since 1998. However, risk-based testing strategy has yielded suboptimal results in identifying HCV-infected persons; a number of studies have found that providers lacked knowledge about HCV prevalence, natural history, diagnostic tests and treatment, and recommendations for testing. Moreover, only 55% of persons with HCV infection reported known exposure risk, and the remaining 45% reported no recognized exposure risk.[10] In 2012, CDC also expanded routine screening for HCV infection to include persons born between 1945-1965.[10]

The Institute of Medicine has identified deficiencies in knowledge and awareness, surveillance, immunization, and services for viral hepatitis in the United States, and recommended strategies to optimize prevention and control of HBV and HCV, policies fully endorsed by the Department of Health and Human Services and CDC.[1,3,10] Early diagnosis of chronic HBV and HCV infections can lead to improved therapeutic response, lower viral loads, halt progression to cirrhosis, and prevent HCC. Immunization should also be recommended for non-immune persons at risk for HBV exposure, household members, and sexual contacts of HBV-infected individuals.

Specialists in fields with expertise in hepatitis and who may evaluate patients for reasons such as international travel — including those in travel and tropical medicine, infectious diseases, and gastroenterology — can reach this broader population that needs to be screened. Through the collaboration of specialists with primary care providers, significant improvement of screening in high-risk populations is achievable. ■

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Delayed Primary Epstein-Barr Virus Infection: Clinical and Immunologic Manifestations

ABSTRACT & COMMENTARY

By Richard R. Watkins, MD, MS, FACP

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Dr. Watkins reports no financial relationships relevant to this field of study.
This article originally appeared in the February 2013 issue of Infectious Disease Alert.

Synopsis: *A prospective study on Epstein-Barr virus seronegative college freshmen found that primary infection was symptomatic in 89% of cases. Kissing was the primary risk factor for infection, and blood viral load, CD8+ lymphocytosis, and IL-6 levels correlated with disease severity.*

Source: Balfour HH, et al. Behavior, virologic, and immunologic factors associated with acquisition and severity of primary Epstein-Barr virus infection in university students. *J Infect Dis* 2013;207:80-88.

In the United States, approximately 50% of individuals develop antibodies to Epstein-Barr virus (EBV) by age 5. Infections during the first decade are usually asymptomatic, while disease is most commonly diagnosed in adolescents of higher socioeconomic status. Researchers at the University of Minnesota sought to determine the proportion of delayed primary infections that are symptomatic. Another goal was to investigate how CD8+ lymphocytosis correlated with symptomatic disease.

Two freshman classes were followed prospectively throughout their undergraduate years. Of 202 EBV antibody-negative students, 143 (71%) were enrolled in the surveillance phase. They were seen every 8 weeks while in school and during breaks if they remained in the area. The visits involved obtaining a medical history, an oral wash specimen, a 40 mL venous blood sample, and completion of a health questionnaire. Sera collected were tested for EBV antibodies. Subjects who developed signs and symptoms suggestive of acute EBV infection were seen as soon as possible and study specimens and questionnaires were obtained. Primary EBV infection was defined as a positive result of an EBV antibody test and the presence of EBV DNA in the oral and/or blood compartment of a subject who was previously negative for both EBV antibodies and EBV DNA. Primary EBV infection was classified clinically as infectious mononucleosis (with at least two of the following: sore throat, cervical lymphadenopathy, fever, and fatigue), symptomatic (symptoms present but did not fulfill the definition of infectious mononucleosis), or asymptomatic. Severity of illness was graded from 0 (asymptomatic) to 6 (essentially bedridden).

Sixty-six out of 143 students developed primary EBV infection during the 4 years of observation. The incidence of infection during the freshman year (26 cases/100 person-years) was more than twice the mean incidence during the following 3 years (10 cases per 100 person years; $P = 0.002$). The incidence was greater in women than men (23.6 vs 16.1 cases/person-years) but was not statisically significant. Sexual behavior was a risk factor for primary

EBV infection, with students reporting deep kissing with or without coitus having similar distributions of time to infection. Infectious mononucleosis developed in 51 subjects (77%). It was symptomatic but not meeting the definition of mononucleosis in eight subjects (12%), and seven asymptomatic (11%). EBV DNAemia was documented in 42 subjects (64%). Heterophile antibodies were documented in 50 (77%) of 65 subjects, IgM antibodies in 54 (83%) of 65 subjects, and IgM antibodies were found as early as 8 days before symptoms began and persisted as long as 420 days after symptom onset.

The authors quantified CD8+ T-cell numbers and activation over time. CD8+ T-cell numbers increased the most during the first 2 weeks following symptom onset. They also observed an upregulation of CD38, HLA-DR, and granzyme B on total CD8+ T-cells in the first 2 weeks. Moreover, the investigators discovered an expansion of natural killer (NK) cells in the blood during acute disease correlated with CD8+ T-cell numbers. Severity of disease corresponded with the quantity of EBV in whole blood, CD8+ T-cell numbers and granzyme B expression. Of several cytokines evaluated during acute infection (including interferon y), only IL-6 correlated significantly with severity of disease.

■ COMMENTARY

As mentioned in an accompanying commentary, what sets this study apart from others on primary EBV infection is the rigor of the prospective follow-up.[1] The investigators should be commended for a study design that involved 143 participants who gave oral and blood samples every 8 weeks over a period of 4 years, and donated additional samples whenever they developed a febrile illness. Sixty-six of them acquired primary EBV infection, of which 89% were symptomatic. This result is much greater than the approximately 25-50% incidence of symptomatic primary EBV infection reported in prior studies. Thus, it seems likely the results of the present study reflect the true incidence of symptoms of primary infection in this age group. Deep kissing was identified as the main risk factor for EBV acquisition, as students who engaged in this activity had similar conversion rates whether or not they engaged in sexual intercourse, and those with no history of kissing remained seronegative.

A prior study found that NK cell numbers correlated with less severe illness, not more as the present study reported.[2] This discrepancy could be due to the smaller numbers of patients in the older study, which lacked internal controls for NK cell numbers and frequency before, during, and after primary EBV infection. Furthermore, data from the current report suggest that both NK cells and CD8+ T-cells respond similarly to the intensity of viral challenge. It is possible that a particular subset of NK cells is responsible for better viral control and symptom reduction, and further research on this topic seems warranted. Indeed, future prospects for an EBV vaccine hinge on our continued elucidation of these complex host-virus interactions. ■

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Contemporary Prevalence of Atherosclerosis in Military Personnel at Autopsy

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

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Dr. Boyle reports no financial relationships relevant to this field of study. This article originally appeared in the February 2013 issue of Clinical Cardiology Alert.

Synopsis: *Among deployed U.S. service members who died of combat or unintentional injuries and received autopsies, the prevalence of atherosclerosis varied by age and cardiovascular risk factors.*

Source: Webber BJ, et al. Prevalence of and risk factors for autopsy-determined atherosclerosis among U.S. service members, 2001-2011. *JAMA* 2012;308:2577-2583.

AUTOPSY STUDIES FROM THE KOREA AND VIETNAM WARS, which demonstrated that atherosclerosis begins in teens and young adults, have revolutionized our understanding of the pathogenesis and progression of coronary artery disease (CAD). Mortality from ischemic heart disease has declined in the United States since then. To determine the prevalence of CAD in young adults in the modern era, Webber and colleagues present data from the autopsies of persons serving the U.S. military from 2001-2010. They linked data from the autopsy reports of all U.S. service members who died of combat or unintentional injuries with the demographic and medical encounter data from the Defense Medical Surveillance System. Hearts were visually inspected for the presence of CAD in the major epicardial coronary arteries, and this was clas-

sified according to the following scheme: minimal (fatty streaking only), moderate (10-49% luminal narrowing of ≥ 1 vessel), and severe (≥ 50% narrowing of ≥ 1 vessel). The presence of aortic atherosclerosis was also noted. To assess the contribution of risk factors to age-adjusted prevalence of atherosclerosis, the authors present the data as age-adjusted prevalence ratios (PR).

A total of 3832 autopsy results were included, with the subjects ranging in age from 18-59 years (mean, 25.9 years), with 98.3% males. The prevalence of any CAD was 8.5%; severe CAD was present in 2.3%, moderate in 4.7%, and minimal in 1.5%. The prevalence of aortic atherosclerosis was 5.7%. The prevalence of any atherosclerosis (i.e., either coronary or aortic atherosclerosis or both) was 12.1%. Those with atherosclerosis were older (mean age 30.5 ± 8.1 years vs 25.3 ± 5.6 years; $P < 0.001$). Those ≥ 40 years had about seven times the prevalence of disease as compared with those ≤ 24 years (45.9% vs 6.6%). Atherosclerosis prevalence was higher in those with risk factors. The prevalence of any atherosclerosis in those with no risk factors was 11.1%, whereas in those with dyslipidemia it was 50.0% (PR, 2.09), in those with hypertension 43.6% (PR, 1.88), and in those with obesity 22.3% (PR, 1.47). Smoking was not associated with a higher prevalence of atherosclerosis. The authors conclude that among deployed U.S. service members who died of combat or unintentional injuries and received autopsies, the prevalence of atherosclerosis varied by age and cardiovascular risk factors.

■ COMMENTARY

This study demonstrates a much lower rate of CAD (8.5%) in military autopsies than was shown in the Korean (77%) and Vietnam (45%) wars. This suggests a significant reduction in the prevalence of atherosclerosis in young U.S. service personnel. This may be due to a true decline in the prevalence of atherosclerotic disease, or it may also be influenced by methodological differences between the different studies. The earlier reports were from the era of conscription, when smoking rates were higher, and the rate of autopsy was approximately 1%. The current study is from this century, from a time of voluntary enlistment, and has a > 60% autopsy rate. There are likely significant biases and methodological differences between studies, but the current study is encouraging that the prevalence of CAD is declining. It is enticing to speculate that lower smoking rates or better education about lifestyle choices have beneficially impacted our communities. Alternatively, we may just be seeing the natural history of the rise and fall of prevalence as seen in any epidemic. Regardless, CAD remains a leading cause of morbidity and mortality in the United States. Any decline in the prevalence of atherosclerosis is most welcome news. ■

Pharmacology Update

Ospemifene Tablets (Osphena™)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

A SELECTIVE ESTROGEN RECEPTOR MODULATOR (SERM), ALSO known as an estrogen agonist/antagonist, has been approved by the FDA for the treatment of dyspareunia (painful intercourse) in postmenopausal women. Ospemifene is manufactured by Penn Pharmaceuticals Services Ltd. and marketed by Shionogi Inc. as Osphena.

Indications

Ospemifene is indicated for the treatment of moderate-to-severe dyspareunia.[1]

Dosage

The recommended dose is one tablet (60 mg) taken orally once daily with food.[1] Ospemifene is available as 60 mg tablets.

Potential Advantages

Ospemifene may carry a lower risk of stroke and deep vein thrombosis than estrogen therapy.[2]

Potential Disadvantages

Ospemifene carries a box warning for increased risk of endometrial cancer similar to unopposed estrogen but may be less than that of tamoxifen.[1,3]

Comments

Vulvovaginal atropy due to menopause is a result of loss of estrogen. Vaginal scraping in postmenopausal women shows a predominance of parabasal cells, decline in superficial squamous cells, and increase in vaginal pH.[4] Ospemifene an estrogen agonist/antagonist has an estrogen-like effect on the vaginal epithelium.[3,4] It was evaluated in patients with moderate-to-severe symptoms in three randomized, placebo-controlled trials.[1,5,6] Two were 12-weeks' duration and one was a 52-week, long-term safety trial. The study population was generally healthy women, age 41-81 years, with baseline superficial cells on the vaginal smear ≤ 5%, vaginal pH > 5, and who had identified at least one of

the following moderate-to-severe symptoms to be the most bothersome: vaginal dryness, pain during intercourse, or vaginal irritation/itching. In trial 1, subjects were randomized to ospemifene 30 mg, 60 mg, or placebo, and in trial 2, ospemifene 60 mg or placebo. Coprimary endpoints were change from baseline to week 12 of the most bothersome symptom (MBS), percent of vaginal superficial and parabasal cells on a vagina smear, and vaginal pH. MBS was self-reported on a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe). Subjects were provided with a non-hormonal lubricant for use as needed. All analyses were conducted on an intent-to-treat basis with last-observation-carried forward. In trial 1 (n = 826), the decrease in symptom score for subjects reporting MBS of vaginal dryness were statistically significant for both strengths of ospemifene compared to placebo. For MBS of dyspareunia, only the 60 mg dose was statistically significant. Significant increase in the percent of superficial cell, decrease in parabasal cells, and decrease in vaginal pH occurred with both strengths. In trial 2 (n = 919), subjects were randomized to ospemifene 60 mg or placebo. Statistically significant improvement from baseline was shown in moderate-to-severe MBS of dyspareunia compared to placebo, (-1.55 vs -1.29, $P < 0.0001$).[1,6] Thirty-eight percent (38%) of subjects reported no vaginal pain with sexual activity compared to 28% for placebo. Fifty-three percent (53%) of subjects showed a two-to-three level improvement in severity compared to 39%. Similar to trial 1, there were significant decreases in parabasal cells (-38% vs. 0.3%) and vaginal pH (-0.82 vs -0.15) and a significant increase in superficial cells (13% vs 2%) compared to placebo by week 4. Long-term follow-up (52 weeks) data suggest that ospemifene had no significant endometrial changes and was well tolerated.[1,7] The most frequently reported adverse events (vs placebo) were hot flashes (7.5% vs 2.6%), vaginal discharge (3.8% vs 0.3%), and muscle spasm (3.2% vs 0.9%). There are currently no published studies comparing ospemifene with topical or systemic estrogens.

Clinical Implications

Dyspareunia is among the most frequently reported problems reported by postmenopausal women with vulvovaginal atrophy.[2,4] Current hormonal treatment includes vaginal or systemic estrogen therapy. Non-hormonal therapies include vaginal moisturizers or lubricants.[4,8] Ospemifene provides an alternative for women with moderate-to-severe dyspareunia. Ospemifene is expected to be available by June 2013. The cost is currently not available. ■

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CME Objectives

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

CME Questions

1. **In comparison to warfarin in atrial fibrillation patients with reduced renal function, apixaban decreases:**
   a. stroke rates.
   b. major bleeding episodes.
   c. total mortality.
   d. All of the above

2. **Chronic hepatitis B and chronic hepatitis C infections:**
   a. can usually be detected by review of exposure risks.
   b. are uniformly screened for in persons with private health insurance.
   c. have newer antiviral therapies that can lead to sustained viral response.
   d. occur rarely in Western developed countries such as the United States.

3. **The incidence of CAD at autopsy in U.S. military personnel today is:**
   a. 8.5%.
   b. 16%.
   c. 25%.
   d. 50%.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is an advisor for Endo, Kowa, Pricara, and Takeda.

A More Effective Regimen for *H. pylori* Eradication

Source: Liou JM, et al. *Lancet* 2013; 381:205-213.

In the United States, peptic ulcer disease is caused primarily by two culprits: nonsteroidal anti-inflammatory drugs and *Helicobacter pylori* (and their combination). Evolution of pharmacotherapy for *H. pylori* currently employs combinations of amoxicillin (AMOX), metronidazole (METR), clarithromycin (CLAR), and a proton pump inhibitor (PPI). Unfortunately, over time *H. pylori* eradication rates with such regimens have fallen to as low as 80% or less. Is there a better way?

Liou at al randomized *H. pylori*-positive Taiwanese adults (n = 900) to one of three regimens — 1) Sequential 10 days: PPI + AMOX for 5 days followed by PPI + CLAR + METR for 5 days; 2) Sequential 14 days: PPI + AMOX for 7 days followed by PPI + CLAR + METR for 7 days; or 3) Standard 14 days: PPI + AMOX + CLAR for 14 days. The PPI used in this clinical trial was lansoprazole.

Adverse effect profiles of the three regimens were similar. Eradication rates were statistically significantly higher using sequential regimens (10 days = 87%, 14 days = 91%) than in standard regimens (82%).

Reflecting an increased recognition of problematic CLAR resistance at the end of the initial comparison trial, treatment failures from each regimen were assigned to receive an additional 14-day sequential course of treatment in which levofloxacin was substituted for CLAR. Eradication rates from this "rescue" population (regardless of which initial regimen they had received) were 80%.

Based on this large dataset, the authors suggest that sequential treatment regimens should become first line. ■

Uric Acid: How Much of a Bad Guy?

Source: Rosendorff C, et al. *J Clin Hypertens* 2013;15:5-6.

Uric acid (URA) has become the object of intense scrutiny of late, with more than its share of accusations linking it to hypertension and heart disease. The relationship between URA and gout is incontrovertible, though not necessarily universal. That is, in persons who develop gout, risk of future attacks is definitely related to absolute URA plasma levels. However, among persons without gout, elevations of URA appear to be well tolerated without evident toxicity in most: In asymptomatic adults with URA levels > 9.0 mg/dL, only about 5% per year go on to manifest acute gout.

The association of URA with hypertension, myocardial infarction, and even congestive heart failure is acknowledged. Whether this relationship is *causal*, and if a causal relationship is determined, whether lowering of URA will be beneficial remains to be determined. Remember the enthusiasm attendant to the recognition that homocysteine was associated with cardiovascular disease, heightened by the assurance that lowering homocysteine was simple and safe (B vitamins and folate), soon thereafter torpedoed by the interventional trials that failed to show improved outcomes in subjects whose homocysteine levels were reduced?

Despite the growing enthusiasm for criminalizing URA, we still do not have a large randomized, controlled trial indicating that modulation of URA improves hard endpoints. Until then, since all medications that reduce URA have their own bundle of potential misadventure to consider, we should watch and wait. ■

The Word 'GPR40 Modulator' May Soon be Entering Our Vocabulary

Source: Basu A, et al. *Diabetes Care* 2013;36:185-187.

The search for safe and effective agents to treat type 2 diabetes (DM2) continues, with hypoglycemia often being a limiting adverse effect of otherwise highly efficacious agents.

It has been observed that free fatty acids (FFA) play a role in glucose homeostasis, although the story line is complex. Acutely, elevations of FFA *stimulate* beta cell secretion of insulin. *Chronic* FFA elevations result in an impaired insulin response to high glucose levels, a phenomenon known as lipotoxicity.

The mechanism by which FFA impacts insulin secretion has been elegantly worked out and includes the G-protein-coupled receptor (GPR40). Because GPR is involved not only in insulin secretion, but also plays a role in obesity and dyslipidemia, its potential as a multimodal intervention has looked promising.

Studies in humans have shown that GPR40 agonists live up to the expectation that they lower glucose, with a very low risk of hypoglycemia. For instance, a head-to-head comparison with the sulfonylurea glimepiride found hypoglycemic episodes to be six-fold lower with the GRP40 agonist.

In an era of a burgeoning population of DM2 patients, we look forward to the addition of pharmacotherapies that safely complement our current options. ■

In Future Issues:

Accuracy of Electronically Reported 'Meaningful Use' Clinical Quality Measures: A Cross-sectional Study

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

Is This the End of the Road for Calcium Supplementation?

In this issue: Calcium supplementation in women; type 2 diabetes treatments and pancreatitis risk; treating chronic idiopathic urticaria; rivaroxaban and VTE; and FDA actions.

High calcium intakes in women

Another study suggests that calcium supplementation may lead to excess all-cause mortality and cardiovascular disease in otherwise healthy women. Researchers studied more than 61,000 Swedish women for 19 years. Diet and calcium intake, including calcium supplementation, were assessed with the primary outcome being death from all causes and cause-specific cardiovascular disease, ischemic heart disease, and stroke. Higher *dietary* intake of calcium (> 1400 mg/day) was associated with a higher death rate from all causes compared to intake between 600-1000 mg/day (hazard ratio [HR], 1.40; 95% confidence interval [CI], 1.17-1.67). Higher calcium intake was also linked to increased risk of cardiovascular disease (HR, 1.49; CI, 1.09-2.02) and ischemic heart disease (HR, 2.14; CI, 1.48-3.09). There was no higher risk of stroke. Intake of calcium in tablet form > 1400 mg/day was associated with 2.5 times greater risk of death from all causes (HR, 2.57; CI, 1.19-5.55). The authors conclude that higher intakes of calcium in women are associated with higher death rates from all causes as well as increased rates of cardiovascular disease but not stroke (*BMJ* published online Feb. 13, 2013. DOI: org/10.1136/bmj.f228). Previous studies have focused more on stroke risk associated with calcium showing mixed results. This well-done study, along with previously published data from the Women's Health Initiative, provides ample evidence to rethink calcium supplementation for the 60% of middle-aged and older American women who are regular users of calcium supplements. The U.S. Preventive Services Task Force came to the same conclusion (even before this study was published) with publication of updated guidelines in February stating that "current evidence is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplements for the primary prevention of fractures in postmenopausal women or men." They further state there is no evidence to support use of more than 1000 mg of calcium and 400 mcg of vitamin D per day and recommends against using doses lower than 1000 mg of calcium and 400 mcg of vitamin D. Their rationale is that supplementation does not reduce fracture risk but does increase the risk of renal stones in otherwise healthy women. This does not apply to women with osteoporosis or vitamin D deficiency (*Ann Intern Med*, published online Feb. 26, 2013). ■

Diabetes therapies and pancreatitis risk

Glucagonlike peptide 1 (GLP-1) mimetics (e.g., analogs of GLP-1 and dipeptidyl peptidase IV inhibitors) used for the treatment of type 2 diabetes might increase the risk of pancreatitis, according to a recent population-based, case-control study. Using a large population database of

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type 2 diabetics, 1269 cases of acute pancreatitis were identified and those patients were matched with 1269 controls with similar risk factors (age, sex, diabetes mellitus complications, etc). After adjusting for available confounders, current use of GLP-1 based therapies (exenatide [Byetta] and sitagliptin [Januvia]) more than doubled the risk for acute pancreatitis (adjusted odds ratio 2.24, 95% CI, 1.36-3.68). The authors state that "Our findings suggest a significantly increased risk of hospitalization for acute pancreatitis associated with the use of sitagliptin or exenatide among adult patients with type 2 diabetes mellitus" (*JAMA Intern Med* published online Feb. 25, 2013. DOI: 10.1001/jamainternmed.2013.2720). Both drugs already carry a boxed warning regarding pancreatitis. ■

Omalizumab for idiopathic urticaria

Chronic idiopathic urticaria is one of the most frustrating entities to treat as many patients do not respond to antihistamines, even in high doses. Now, a new study suggests that omalizumab (Xolair), an IgE monoclonal antibody used to treat asthma, may be effective in these patients. Patients with moderate-to-severe chronic idiopathic urticaria (n = 323) were randomized to SQ injections of omalizumab every 4 weeks for three total injections at doses of 75 mg, 150 mg, 300 mg, or placebo. The primary outcome was itch-severity score. The 75 mg dose was no better than placebo, but the two higher doses showed significant reductions in itching, with the 300 mg dose being the most effective. The higher dose was also associated with the highest risk of side effects, however, at about 6%. The authors conclude that omalizumab was effective in these patients who were previously symptomatic despite antihistamines. The study was sponsored by the drug manufacturers Genentech and Novartis Pharma (*N Engl J Med* published online Feb. 24, 2013. DOI: 10.1056/NEJMoa1215372). ■

Rivaroxaban for VTE prevention

Rivaroxaban, the oral Xa inhibitor, is as effective as enoxaparin in preventing venous thromboembolism (VTE) in patients with acute medical illnesses, but with a higher risk of bleeding, according to a new study. More than 8100 acutely ill hospitalized patients were randomized to 10 days of enoxaparin 40 mg SQ daily or 35 days of rivaroxaban 40 mg orally with matching placebos. The primary outcome of asymptomatic or symptomatic VTE occurred in 2.7% of patients in both groups by day 10. By day 35, the rates were 4.4% for rivaroxaban and 5.7% for enoxaparin ($P = 0.02$). However, the bleeding rate was more than double in the rivaroxaban group at day 10 (2.8% vs 1.2%, $P < 0.001$) and even higher at day 35 (4.1% vs 1.7%, $P < 0.001$). The authors conclude that rivaroxaban was noninferior to enoxaparin for standard duration thromboprophylaxis (10 days) and reduced the risk of VTE at 35 days with an increased risk of bleeding (*N Engl J Med* 2013;368:513-523). ■

FDA actions

A new selective estrogen receptor modulator (SERM) has been approved for the treatment of dyspareunia due to vulvar and vaginal atrophy in postmenopausal women. Ospemifene appears to benefit vaginal epithelium without significant effect on the endometrium. The drug's safety and efficacy was established in three clinical trials of nearly 1900 postmenopausal women with vulvar and vaginal atrophy who were randomly assigned to ospemifene or placebo. After 12 weeks, the first two trials showed statistically significant improvement in dyspareunia while the third trial supported the long-term safety of the drug. The drug is contraindicated in women with genital bleeding, estrogen-dependent cancer, or thromboembolic disease. The risk of stroke and VTE was higher than baseline but lower than the rates seen with estrogen replacement therapy. Ospemifene comes with a boxed warning regarding endometrial hyperplasia and abnormal vaginal bleeding. Common side effects include hot flashes, vaginal discharge, muscle spasms, and sweating. It will be marketed by Shionogi Inc. as Osphena.

The FDA has approved ado-trastuzumab emtansine for use as a single agent in patients with late-stage, HER2-positive breast cancer. The drug is approved for patients who have already been treated with trastuzumab and taxane separately or in combination. Approval was based on a study of nearly 1000 women with metastatic breast cancer in which progression-free survival was about 3 months longer with the drug compared to lapatinib plus capecitabine, and overall survival was about 6 months longer. Ado-trastuzumab emtansine is marketed by Genentech as Kadcyla. ■