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Risk of Bleeding with Warfarin Therapy for Atrial Fibrillation

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

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Dr. DiMarco does research for Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific. This article originally appeared in the January 2013 issue of Clinical Cardiology Alert.

Synopsis: *The authors conclude that in a large cohort of older patients with atrial fibrillation, hemorrhage is common during both the first 30 days and subsequent months of warfarin therapy, and is related to risk factors in the CHADS2 score and also to age.*

Source: Gomes T, et al. Rates of hemorrhage during warfarin therapy for atrial fibrillation. *CMAJ* 2013;185:E121-E127.

THIS PAPER DETAILS THE RESULT OF A POPULATION-BASED COHORT STUDY of all Ontario, Canada, residents older than 66 years of age who began warfarin therapy for atrial fibrillation over an 11-year period. Patients were identified by the authors from data in the Ontario Health Insurance Plan. Patients were included if they had a hospital or office visit diagnosis of atrial fibrillation and began warfarin during this time period. Medical records were then surveyed for the occurrence of major hemorrhages. This was defined as a visit to an emergency department or admission to a hospital for hemorrhage during warfarin therapy. Patients were followed for up to 5 years after starting warfarin. Hemorrhage was classified by anatomic site using standard definitions. If patients had more than one admission for hemorrhage, only the first event was included.

During the 13-year study period, there were 125,195 patients who began therapy with warfarin in the setting of a diagnosis of atrial fibrillation. This was 47% of all new users of warfarin in this age group during this time period. Of these patients, 69% had an estimated $CHADS_2$ score ≥ 2. In this inception cohort, the cumulative incidence of hemorrhage

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was 1.0% at 30 days, 4.1% at 1 year, and 8.7% at 5 years. During the study, the overall risk of hemorrhage was 3.8% per patient year. The annualized risk was highest during the first 30 days of therapy (11.8%) and 3.4% during the follow-up period. Hemorrhage was more common as the $CHADS_2$ score increased. Patients with a $CHADS_2$ score ≥ 4 had a 16.7% hemorrhage rate per person year in the first 30 days and 6.0% per year afterwards. By contrast, those with $CHADS_2$ scores < 2 had hemorrhage rates of 1.8% per person year with a score of 0 and 2.5% per person year with a score of 1. Hemorrhage rates were higher among patients older than 75 years (4.6% in older patients vs 2.9% in younger patients). Upper and lower gastrointestinal hemorrhage accounted for 63% of the hemorrhage-related hospitalizations, intracranial hemorrhage for 5%, and other sites, mostly genitourinary, for 39%. There were 1963 deaths due to hemorrhage in the hospital or within 7 days after discharge. Intracranial hemorrhage had the highest mortality (41.7%) compared to gastrointestinal hemorrhage (14.7%) and other sites of hemorrhage (12.6%).

The authors conclude that in a large inception cohort of patients with atrial fibrillation, hemorrhage is common during both the first 30 days and subsequent months of warfarin therapy and is related to risk factors in the $CHADS_2$ score and also to age. The risk of hemorrhage is higher than has been seen in recent published randomized trials of anticoagulation therapy. The mortality rate associated with hemorrhage, particularly intracranial hemorrhage, is extremely high.

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Questions & Comments
Please call **Neill Kimball**, Managing Editor, at (404) 262-5404.

■ **COMMENTARY**

Since the new oral anticoagulants, dabigatran and rivaroxaban, were approved for stroke prevention in patients with atrial fibrillation, concerns have been raised about bleeding problems with these agents that had not been prominent in the randomized clinical trials. Reports in both the medical literature and the lay press have complained that the level of anticoagulation cannot be monitored with standard tests and that there is no available rapid antidote. Although these statements about the new oral anticoagulants are true, this paper points out that bleeding with warfarin is also a major concern. Particularly striking are the very high rates of bleeding with warfarin during the first month of therapy and the shockingly high mortality rates seen during hospitalizations for hemorrhage. We have scoring systems for both stroke risk and bleeding risk in patients on anticoagulant therapy. The data in this paper indicate that applying these risk scores in clinical practice is still problematic. ■

Mammography: Does Early Detection Matter?

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH

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Dr. Jensen is a consultant for Bayer Healthcare and Population Council; is a speaker for Bayer Healthcare and Merck; receives research support from Agile Pharmaceuticals, Bayer Healthcare, HRA Pharma, Merck, and Population Council; and is on the advisory boards of Bayer Healthcare, Merck, HRA Pharma, and Agile Pharmaceuticals. This article originally appeared in the January 2013 issue of OB/GYN Clinical Alert.

Synopsis: *Although widespread screening mammography has greatly increased the diagnosis of early breast cancer, it has had only a marginal effect on the diagnosis of late-stage tumors and breast cancer mortality.*

Source: Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med* 2012;367:1998-2005.

To evaluate the effectiveness of mammography as a screening test, the authors used the Surveillance, Epidemiology, and End Results (SEER) database to examine trends from 1976 through 2008 in the incidence of early-stage breast cancer (ductal carcinoma in situ and localized disease) and late-stage breast cancer (regional and distant

disease) among women 40 years of age or older in the United States. During this time interval, screening mammography was associated with a doubling in the number of cases of early-stage breast cancer detected each year, from 112 to 234 cases per 100,000 women: an absolute increase of 122 additional breast cancer cases per 100,000 women. At the same time, the rate at which women presented with late-stage cancer decreased by only 8%, from 102 to 94 cases per 100,000 women: an absolute decrease of just 8 cases per 100,000 women. The authors concluded that with the assumption of a constant underlying disease burden (e.g., no change in the biology or virulence of breast cancer), only 8 of the 122 additional early-stage cancers diagnosed by mammography would have been expected to progress to advanced disease. In other words, according to these data, most of the tumors detected by screening would never have led to clinical symptoms or required treatment of any kind. After adjusting the numbers for the transient excess cancer incidence associated with hormone-replacement therapy and for trends in the incidence of breast cancer among women younger than 40 years of age, the authors estimated that routine screening mammography has led to the "overdiagnosis" and treatment of breast cancer in 1.3 million U.S. women over the past 30 years. They estimated that in 2008 alone, breast cancer was overdiagnosed in more than 70,000 women, just under one-third of all breast cancers diagnosed.

■ COMMENTARY

Many American women and their doctors sat down on Thanksgiving Day confronted with new information questioning whether screening mammography is one of the things for which they should be thankful. During the last 30 years, considerable effort has led to broad acceptance of routine screening mammography as an essential health care service, with mandated coverage now the law of the land. Effective screening programs are widely supported because breast cancer is a pernicious and indiscriminate killer that takes our mothers, sisters, daughters, wives, and friends. With few options for effective treatment of advanced breast cancer, early detection and treatment has understandably been the focus of attention for many advocacy groups. However, the goal of screening is the detection of life-threatening disease at an earlier, more curable stage. Therefore, the effectiveness of cancer-screening programs should be judged not just by the increase in the incidence of cancer detected at an early stage, but also by a decrease in the incidence of cancer presenting at a late stage and a reduction in overall mortality.

Bleyer and Welch used the SEER database to investigate the hypothesis that routine screening mammography starting at age 40 is an effective screening strategy. Their conclusions that yearly tests lead to a large increase in diagnosis of early tumors but do not reduce the diagnosis of advanced tumors or greatly impact breast cancer mortality support the earlier recommendations against annual routine screening mammography starting at age 40 published by the U.S. Preventive Health Task Force (USPHTF) in 2009.[1]

Although screening mammography substantially increases the number of cases of early-stage breast cancer detected, unlike cervical cancer screening, this has only marginally reduced the rate at which women present with advanced cancer. This leads to two questions: 1) Does the benefit of routine screening mammography outweigh the potential for harm? and 2) Should the health care dollars invested in screening be redirected instead to research and treatment of clinically important tumors?

The answer to the first question is the clinical point that you will need to address with each women age 40 or older in the office. It is important to acknowledge that we do not have a highly sensitive and specific method of screening for advanced breast cancer. Although we recognize that mammography is not perfect, the relief most women experience with a negative test is considerable. Unfortunately, an uncomfortably common result is a "positive" screening examination and the sequence of events that stems from this. Although routine annual mammograms starting at age 40 instead of age 50 and continued to age 69 do reduce breast cancer mortality, the overall effect is small. This strategy will prevent one additional cancer death (8.3 vs 7.3) for every 1000 women screened at the expense of 63 more "unnecessary" biopsies.[2] You and your patient need to decide if a 6% chance of getting a biopsy is worth the 0.1% chance of avoiding cancer mortality associated with annual screening at age 40 (recommended by ACOG and the American Cancer Society) or age 50 (recommended by the USPHTF). There will be 70 fewer biopsies in 1000 women age 40-69 who get mammograms every other year compared to annually, but two additional women will die from breast cancer.[2] So if you are willing to risk more intervention, mammography does reduce the risk of breast cancer mortality, although the effect is small. Many women gladly will accept the high burden of a breast biopsy to reduce the chance of breast cancer death. But this is personal and should be discussed in real terms with each patient.

On the flip side, the high "false-positive" rate and anxiety during the work-up of a positive screen should not be underestimated. Furthermore, the data from Bleyer and Welch suggest that the majority of early breast cancers detected may never become clinically important. Their results suggest that in 2008 more than 70,000 women (accounting for one-third of all breast cancer diagnoses in women ≥ 40) were "overdiagnosied" (e.g., the cancer diagnosed would never have progressed to clinically impor-

tant disease). If true, this represents a substantial harm of even most "true-positive" screening mammogram results.

The second question has enormous public health impact in our role as advocates for all women, not just the patient in front of us. Considerable evidence suggests that the reduction of breast cancer mortality observed over the last 30 years is due more to effective treatment than to early detection.[3] Bleyer and Welch concluded that the impact of early detection on decreasing numbers of deaths must be small because the absolute reduction in deaths (20 deaths per 100,000 women) observed during the 30-year study period is larger than the absolute reduction in the number of cases of late-stage cancer (eight cases per 100,000 women). Furthermore, they point out that this small reduction in cases of late-stage cancer is confined to regional (largely node-positive) metastatic disease. In other words, screening mammography did not influence the number of women presenting with advanced metastatic disease.

According to the 2010 census, there are more than 52 million women aged 40-65, and the average cost of a mammogram is $266.[4] The math tells us that a universal annual screening mammography program will cost almost $14 billion, and this does not include the cost of follow-up imaging studies and biopsy procedures for "false-positive" studies or for the treatment cost of "overdiagnosed" tumors. Imagine a $14 billion dollar investment in research into better diagnostics and treatment for truly life-threatening breast cancers.

Like many OB/GYNs, I spent a large proportion of my early years in practice performing colposcopy and treating early cervical dysplasia. Now we know that cervical cancer is caused by a virus, that screening intervals can be greatly reduced, and that most early lesions do not require treatment at all. I hope that we can see a similar shift in practice with respect to breast cancer screening and treatment in the near future. In the meantime, ACOG and the American Cancer Society still recommend annual screens at age 40. The evidence for annual exams does support a modest benefit to individual women at the expense of unnecessary follow-up and biopsies (and perhaps unnecessary treatment). I am beginning to shift away from a strong advocacy for routine mammography, but only when we agree to shift the resources to a better approach. Breast cancer is a horrible disease. We should all agree that more research is needed. ■

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Risk of Angioedema with Drug Therapy

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 January 2013 issue of Clinical Cardiology Alert.

Synopsis: *The authors concluded that compared to beta-blockers, the risk of angioedema is highest with ACEIs or aliskiren and lowest with ARBs.*

Source: Toh S, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. *Arch Intern Med* 2012;172:1582-1589.

Angioedema is an infrequent, but serious, adverse event from drug therapy. Drugs that affect the renin-angiotensin-aldosterone system have been linked to angioedema, but the relative frequency of this complication with these drugs is poorly understood. Thus, this group of investigators used the FDA's Mini-Sentinel Distribution Database (MSDD) to explore this issue. The MSDD is a pilot program involving 17 health plans for an eventual national system for monitoring the safety of medical products. An inception cohort design was used to assess patients > 18 years old receiving only an angiotensin-converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB), aliskiren, or a beta-blocker (reference group). The primary endpoint was a new diagnosis of angioedema and the secondary outcome was serious angioedema (airway obstruction requiring in-patient care). The study was censured if angioedema occurred, the drug was stopped, another drug in this group was started, or 1 year had passed. There were approximately 1.8 million initiated on ACEIs, 467,000 on ARBs, 4867 on aliskiren, and 1.6 million on beta-blockers. Mean follow-up for ACEIs was 149 days, ARBs 136 days, aliskiren 112 days, and beta-blockers 126 days. Among the approximately 4 million patients studied, there were 4511 cases of angioedema and

388 cases of serious angioedema. The incidences per 1000 persons were 1.79 for ACEIs, 0.62 for ARBs, 1.44 for aliskiren, and 0.58 for beta-blockers. Serious angioedema rates were 0.18 for ACEIs, 0.02 for ARBs, 0.21 for aliskiren, and 0.03 for beta-blockers. The authors concluded that compared to beta-blockers, the risk of angioedema is highest with ACEIs or aliskiren and lowest with ARBs.

■ **COMMENTARY**

This large, well-done retrospective, observational study has important implications for the care of patients. Angioedema and serious angioedema in patients receiving drugs that have been associated with angioedema is rare. Even patients receiving drugs not thought to be associated with angioedema (beta-blockers) have a measurable risk of angioedema. In fact, in this study, the incidence of serious angioedema was higher with beta-blockers than ARBs. The main result of this study is that compared to beta-blockers, ACEIs and aliskiren have a three-fold higher incidence of angioedema and ARBs are 16% higher. Serious angioedema is five times more common with ACEIs vs beta-blockers. This is a robust study involving about 4 million patients among whom more than 50% were women. One limitation of this study is a lack of racial or ethnicity data; African Americans are known to have a higher incidence of angioedema. However, this study did confirm that women and those > age 65 years have higher rates of angioedema with ACEIs, but not ARBs. So, my question at this time is: Is there any reason to use ACEIs vs ARBs, especially in outpatients with hypertension facing decades of therapy? I think not, especially since at least one ARB is now generic. ■

Physicians' Own Beliefs on Goals of Care Influence Presentation of Comfort Care Option to Patient Surrogates

ABSTRACT & COMMENTARY

By Betty Tran, MD, MS

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Dr. Tran reports no financial relationships relevant to this field of study. This article originally appeared in the January 2013 issue of Critical Care Alert.

Synopsis: *During family discussions, physicians who believe more strongly that life support should be withdrawn are more likely to present the option of comfort care and describe its benefits.*

Source: Schenker Y, et al. Association between physicians' beliefs and the option of comfort care for critically ill patients. *Intensive Care Med* 2012;38:1607-1615.

This study conducted in five ICUs at two academic hospitals in San Francisco sought to describe how comfort care is presented to surrogates and if physicians' beliefs on whether life support should be withdrawn are associated with the option of comfort care being presented. One hundred and five physician-family conferences were identified through the ICU nurses, but only 72 were included in the final analysis after excluding conferences in which the physician and/or family declined participation. Each conference was audiotaped and subsequently transcribed verbatim for analysis. The study team coded whether comfort care was presented as an option by the physician, what risks and benefits of comfort care were presented, and what other treatment options (unlimited intensive care or limited intensive care) were offered. Demographic information was collected on patients, surrogates, and physicians. Physicians were also asked immediately after the conference to grade how strongly they believed life support should be withheld or withdrawn prior to the family conference on a scale of 0 (not strongly at all) to 10 (extremely strongly). Coders were blinded to all the participants' questionnaire responses.

The physician-family conferences occurred a mean of 10 days after ICU admission; on average, 60% of the ICU stay had elapsed at the time of the conference. Patients had a mean APACHE II score of 29 on the day of the conference, with the overall inpatient mortality rate being 72% (all due to withdrawal of life support). Comfort care was not presented as an option in 32 of 72 (44%) of the conferences; of these, 78% included only discussion of continued unlimited intensive care. In multivariate analyses, the only variable associated with the presentation of comfort care was the strength of the physicians' belief that life support should be withdrawn (odds ratio [OR] 1.38, 95% confidence interval [CI] 1.14-1.66; $P = 0.01$). In the 40 (56%) of 72 conferences in which comfort care was presented, there was an association between the strength of the physician's belief that life support should be withdrawn and the number of unique benefits of comfort care that were discussed (OR 1.12, 95% CI 1.01-1.25; $P = 0.04$).

■ **COMMENTARY**

In their clinical policy and consensus statements, the American College of Critical Care Medicine and American Thoracic Society support a shared decision-making model that includes surrogates, family members, and the health care team when the patient lacks full decision-making capacity. For example, for technical decisions regarding choice of antibiotics, surrogates overwhelmingly prefer physicians to make the final decision, but when it

comes to life-sustaining treatment decisions, the extent to which the physician is involved is variable and can depend not only on surrogate preferences, but also the physician's own professional judgment and ethics.[1-3]

Thus, depending on the context, although the authors cite their findings as surprising, their results can be viewed as fairly predictable. Physicians may be more likely to present and promote comfort care as an option in cases where they believe no other medical treatment is available or for patients who have a dismal prognosis from a prior underlying condition, such as metastatic cancer or chronic lung disease. On the other hand, physicians may be less likely to present comfort care options in situations they perceive to be potentially reversible. Alternatively, if patients or surrogates have previously expressed their wishes to continue aggressive care, physicians may be more reluctant to raise the option of comfort care. In these situations, the omission of comfort care as an option is not necessarily an oversight on the part of the physician, but may be a conscientious decision based on the clinical scenario. As the authors duly note, the context surrounding the decision not to present comfort care as an option is an important area for future research.

Furthermore, although the authors rightly argue that failure to present comfort care as an option based purely on physicians' beliefs is problematic, the issue of how and when best to present this alternative to surrogates has yet to be answered. The notion that comfort care is "giving up" or "doing less" as opposed to "doing everything" will have to be quelled, and continual, open communication between physicians and surrogates will be necessary to foster trust in the families of critically ill patients and to understand their preferences in the decision-making process. These aims, in addition to improving clinician communication skills in discussing life-sustaining treatment decisions, will enhance the extent to which physicians can support and advise surrogates in the decision-making process. ■

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Pharmacology Update

Lomitapide Capsules (Juxtapid™)

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.

THE FIRST INHIBITOR OF THE MICROSOMAL TRIGLYCERIDE transport protein (MTP) has been approved for the treatment of homozygous familial hypercholesterolemia (HoFH). MTP is a key protein in the assembly and secretion of apolipoprotein B (ApoB)-containing lipoprotein in the liver and intestine.[1] Inhibition of MTP by lomitapide affects the synthesis of chylomicrons and very low-density lipoprotein (VLDL). Lomitapide is marketed by Aegerion Pharmaceuticals as Juxtapid. It is only available through a restricted program, the Juxtapid Risk Evaluation and Mitigation Strategy program.

Indications

Lomitapide is indicated as an adjunct to a low-fat diet (< 20% of energy from fat) and other lipid-lowering treatments (e.g., LDL-apheresis) to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), ApoB, and non-high-density lipoprotein (non-HDL) cholesterol in patients with HoFH.[1]

Dosage

The recommended initial dose is 5 mg once daily.[1] The dose may be titrated to 10 mg once daily after 2 weeks based on safety/tolerability. The dose may be further titrated at a minimum of 4-week intervals to 20 mg, 40 mg, and to a maximum of 60 mg daily. Transaminase levels should be obtained before any dose increase. The dose should be adjusted if alanine (ALT) or aspartate aminotransferases (AST) is three times the upper limit of normal or higher. The capsule should be taken with water and without food at least 2 hours after the evening meal. Daily supplements of vitamin E, linoleic acid, alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid should be taken. In patients with mild liver dysfunction, the dose should not exceed 40 mg per day. Coadministration of lomitapide and moderate or strong inhibitors of CYP3A4 is contraindicated and should not exceed 30 mg/day with weak CYP3A4 inhibitors (e.g., atorvastatin).

Potential Advantages

Familial hypercholesterolemia is difficult to treat. Current lipid-modifying therapies, even combined with LDL-apheresis, rarely achieve optimal LDL levels. Lomitapide offers an option for these patients who are at extremely high risk for cardiovascular disease and premature death.

Potential Disadvantages

Lomitapide has potential for hepatotoxicity.[1] Treatment causes elevation of liver transaminases and increases hepatic fat (hepatic steatosis). ALT and AST should be measured before starting therapy. Gastrointestinal adverse events are common, with diarrhea (79%), nausea (65%), dyspepsia (38%), and vomiting (34%) being most common.[1] Adhering to a low-fat diet reduces the risk of gastrointestinal adverse events. Lomitapide is contraindicated in pregnancy.

Comments

The safety and efficacy of lomitapide was studied in a single-arm, 78-week trial in 29 patients with HoFH.[1,2] This cohort had a mean age of 30.7 years, 55% male, and mainly Caucasian (86%). All patients were either homozygotes or compound heterozygotes for mutations in the LDLR gene or genes affecting LDL-receptor functionality.[2] Treatment included statins (93%) and ezetimibe (76%), and 62% received apheresis. After stabilizing treatment regimens, subjects were initiated on 5 mg daily, and titrated up to 60 mg/day at 4-week intervals based on safety and tolerability (including transaminase levels). The primary endpoint was percent change in LDL-C from baseline at week 26. Twenty-three patients completed the 26-week assessment as well as the 78-week study. Four of six patients discontinued the study due to adverse events. Lomitapide produced statistically significant changes in LDL-C (-40%), TC (-36%), ApoB (-39%), and triglycerides (-45%). While the lipid-lowering effect was reduced at week 78, these remain statistically significant.[2] HDL cholesterol and ApoA-I levels were reduced significantly at week 26, but returned to levels similar to baseline at week 78. Hepatic fat increased from 1% at baseline to 8.6% by week 26 and seemed to stabilize thereafter.[2]

Clinical Implications

HoFH is a functional mutation in both LDL-receptor alleles or those that affect LDL receptor functionality, or skin fibroblast LDL-receptor activity (< 20% or normal, or untreated total cholesterol > 500 mg/dL and triglycerides < 300 mg/dL, and both parents with documented untreated total cholesterol > 250 mg/dL).[1] Treatment includes low-fat diet and other lipid-lowering treatments, including LDL-aphersis. Lomitapide provides another option for patients with this rare, life-threatening condition. The wholesale cost is $18,030 for a 28-day supply of the 10 mg dose and $22,630 for the 20 mg dose. ■

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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 a large Canadian study, the 1-year hemorrhage rate on warfarin for atrial fibrillation was:**
   a. 1%.
   b. 2%.
   c. 4%.
   d. 8%.

2. **Over the last 30 years, routine mammography has been associated with:**
   a. a 50% increase in the diagnosis of early breast cancer and an equivalent reduction in the diagnosis of advanced breast cancer.
   b. a 50% increase in the diagnosis of early breast cancer but a substantially smaller reduction in the diagnosis of advanced breast cancer.
   c. a decrease in breast cancer mortality due principally to an increase in early diagnosis.
   d. fewer unnecessary biopsies and follow-up tests due to the better resolution of digital mammograms.

3. **Although rare, the risk of angioedema is how much more common with ACEIs than beta-blockers?**
   a. 15%
   b. 50%
   c. 100%
   d. 300%

4. **During physician-family conferences on treatment plans, the presentation of comfort care as an option was associated with:**
   a. patient race/ethnicity.
   b. the strength of physicians' beliefs that life support should be withdrawn.
   c. severity of patient illness.
   d. patient length of stay in the ICU.
   e. All of the above

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

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

CKD: Consistency of GFR and Albuminuria as Risk Predictors

Source: Hallan SI, et al. *JAMA* 2012; 308:2349-2360.

Clinicians have become increasingly aware of the disease burden associated with chronic kidney disease (CKD), especially since the routine inclusion of a calculated estimated glomerular filtration rate (eGFR) within metabolic profile testing. Promulgation of CKD stages by national organizations and encouragement of clinicians to consider referral of patients with CKD at an earlier stage (usually by CKD stage 3-B) has prompted the clinical community to address eGFR as well as the presence, absence, and severity of urinary albumin excretion on a more consistent basis. Because of inherent renal functional decline associated with increased age, accompanied by decrease in muscle mass that contributes to the generation of creatinine, some have questioned whether current stratification of CKD by eGFR, albuminuria, or both holds true throughout the lifespan.

Hallan et al performed a meta-analysis on data from more than 2 million individuals in Asia, Australasia, Europe, and North/South America to investigate whether eGFR and the presence of albuminuria remain consistently predictive of adverse outcomes.

Although at older ages the *absolute* risk imparted by CKD was greater than in younger folks (simply because a larger absolute number of older individuals die than younger individuals, whether or not they have CKD), overall, the hazard ratio (HR) for mortality decreased with increasing age. For example, at an eGFR of 45 mL/min, the HR for death (when compared to a normal eGFR) was 3.5 for persons ages 18-54, 2.2 for ages 55-64, and 1.35 for ages > 75 years. A similar relationship was noted for albuminuria.

Albuminuria and reduction in eGFR are associated with adverse outcomes throughout the lifespan, although the HR for risk appears to lessen as we age. ■

Changing Outcomes for Patients with Chronic Hepatitis C

Source: van der Meer AJ, et al. *JAMA* 2012;308:2584-2593.

Chronic hepatitis C (HEPC) has an increased risk for liver cancer, end-stage liver disease, and all-cause mortality. Fortunately, current antiviral treatments for HEPc (e.g., ribavirin and interferon) are effective in the majority of subjects. As many as 80% of HEPc patients who complete a therapeutic course will obtain what is called a sustained virological response (SVR); that is, no detectible HEPc virus 6 months *after* completion of therapy. SVR might reasonably be titled "cure," since indications are that absence of virus at 6 months is indicative of permanent eradication.

Nonetheless, some patients enjoying SVR already have experienced inflammatory hepatic changes resulting in fibrosis. It has not been sufficiently elucidated whether achievement of SVR ultimately reduces risk for mortality, liver cancer, or hepatic failure, especially in a group with already established hepatic fibrosis.

Using an international multicenter database (n = 540), the outcomes of HEPc patients with long-term follow-up (mean 8.4 years), as well as biopsy-proven fibrosis, were investigated to compare those who attained SVR vs those who did not. The mortality rate was essentially three times greater in those who did not attain SVR (26% vs 8.9%); the comparative cumulative incidence rate of liver-related mortality or transplantation was even more dramatic: 1.9% (SVR) vs 27.4% (SVR not attained). The attainment of SVR is associated with substantial long-term reductions in mortality as well as less need for liver transplantation. ■

Is Fructose a Primary Culprit in Obesity?

Source: Page KA, et al. *JAMA* 2013; 309:63-70.

Sorting out the causes of the current pandemic of obesity has not been easy and appears to have contributions from various life quadrants: activity, genetics, absolute calorie ingestion, and — most recently — characteristics of the calories we ingest. For instance, whereas in the recent past one might simplistically think that a gram of ice cream and a gram of broccoli should result in similar metabolic impact, recognition of the glycemic index (variation in glucose rate of absorption from different food sources) has taught us that a calorie is not necessarily always a calorie in the grander scope of things.

Fructose, an increasingly commonplace component of fast foods, snacks, etc., has recently come under fire as a potential culprit exacerbating the obesity pandemic. Mechanistically, fructose could be metabolically detrimental because (compared to glucose, that is) it blunts satiety-inducing GLP-1, and fails to shut off appetite-stimulating ghrelin.

Page et al measured regional cerebral blood flow in response to glucose and fructose ingestion. They found that fructose did not produce the same reduction in hypothalamic cerebral blood flow (associated with satiety and fullness) as did glucose. Disproportionate consumption of fructose may be a significant contributor to weight management problems. ■

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.*

Aspirin Use and Age-Related Macular Degeneration

In this issue: Aspirin use and AMD risk; using NSAIDs and antihypertensive agents; and FDA actions.

Does aspirin cause AMD?

Does regular aspirin use put patients at risk for age-related macular degeneration (AMD)? That is the finding in a highly publicized study from Australia published in *JAMA Internal Medicine* (formerly *Archives of Internal Medicine*). A prospective analysis was conducted from an Australian population-based cohort that included four examinations in 15 years as well as questionnaires regarding aspirin use. Of the 2389 participants with follow-up available, 257 (10.8%) were regular aspirin users and 63 of these (24.5%) developed neovascular (wet) AMD. Regular aspirin users were more likely to develop neovascular AMD: The 15-year cumulative incidence was 9.3% in aspirin users and 3.7% in non-users. After adjustment for age and multiple cardiovascular risk factors, regular users of aspirin had an odds ratio of neovascular AMD of 2.46 (95% confidence interval [CI], 1.25-4.83). The association showed a dose response effect, with daily users at higher risk. Aspirin was not associated with geographic atrophy (dry AMD). The authors conclude that "regular aspirin use is associated with increased risk of incident neovascular AMD independent of a history of cardiovascular disease and smoking." (*JAMA Intern Med* published online Jan. 21, 2013. doi:10.1001/jamainternmed.2013.1583). A related editorial points out that age-related AMD is the leading cause of blindness in Western countries, and this study suggests that regular aspirin is associated with an approximate 2.5-fold greater risk in incident AMD. The study is not a randomized trial, and although there is some biological plausibility in the association between aspirin use and development of AMD, this study is "not sufficiently robust to be clinically directive." (*JAMA Intern Med* published online Jan. 21, 2013. doi:10.1001/jamainternmed.2013.2530.) The take-home message for now is that for patients who are likely to benefit from aspirin (secondary prevention of cardiovascular disease), practice should not change. However, for those patients who take aspirin for indications that are less compelling, we may want to rethink the recommendation until good trials on the relationship between aspirin use and AMD can be assessed. ■

NSAIDs and antihypertensive agents

Mixing certain antihypertensive agents with nonsteroidal anti-inflammatory drugs (NSAIDs) increases the risk of renal failure, according to a new study. In a retrospective cohort study of nearly 500,000 users of antihypertensive drugs in the United Kingdom, rate ratios of acute kidney injury associated with current use of certain antihypertensive agents with NSAIDs were assessed. After a mean follow-up of 5.9 years, 2215 cases of acute kidney injury were identified. Overall, current use of a single antihypertensive (either diuretics, angiotensin-converting enzyme inhibi-

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tors [ACEIs], or angiotensin receptor blockers [ARBs]), along with an NSAID was not associated with increased rate of acute injury. However, combining a diuretic with either an ACEI or ARB along with an NSAID increased the rate of acute kidney injury significantly (rate ratio 1.31, 95% CI, 1.12-1.53). This 31% increased risk of acute kidney injury was driven by a nearly two-fold increased risk in the first 30 days of use. The authors conclude that triple therapy consisting of diuretics with an ACEI or ARB along with an NSAID was associated with an increased risk of acute kidney injury, especially at the start of treatment (*BMJ* published online January 8, 2013. doi.org/10.1136/bmj.e8713). ■

FDA actions

An advisory committee to the FDA has recommended moving hydrocodone/acetaminophen (Vicodin, Norco) from schedule III to schedule II later this year. The move would put the drug in the same category as morphine and oxycontin, and would require a handwritten, tamper-proof prescription for every prescription and refill. Vicodin — the most widely prescribed drug in this country — is at the center of the controversy regarding prescription drug abuse, which has become "epidemic" in this country, according to the CDC. The United States consumes 99% of all the hydrocodone produced worldwide, and deaths attributable to prescription opioid abuse skyrocketed in the last 2 years, outpacing deaths from illegal opioid drugs, including heroin. The move is supported by some advocacy groups, including an endorsement by the American Academy of Pain Medicine, but not by others. Some physicians are concerned that the schedule change will be a major inconvenience for legitimate pain patients and their physicians, who will be required to write a tamper-proof prescription for each refill of the drug.

The FDA has approved an over-the-counter version of topical oxybutynin for the treatment of overactive bladder in women ages 18 and older. The approval is for women only, with oxybutynin available to men by prescription only. The anticholinergic drug has been used for years by prescription for this indication. In studies of more than 5000 subjects, it was determined that consumers can understand the labeling and "properly select whether the product is right for them." Merck will market the product as a patch that is replaced every 4 days under the trade name Oxytrol for Women.

The FDA has lowered the recommended doses for zolpidem (Ambien) for women. The agency based its recommendation on findings that the popular insomnia drug might impair alertness the next morning if taken at recommended doses. The recommendation is also based on findings that zolpidem stays in the body longer than previously thought, especially in women who process the drug somewhat slower. The new recommended maximal dose for women has been lowered from 10 mg to 5 mg for the immediate-release product, and from 12.5 mg to 6.25 mg for the extended-release (Ambien CR). The FDA further recommends that zolpidem and all insomnia drugs should be used at the lowest dose needed to treat symptoms in both men and woman.

The FDA has approved alogliptin for the treatment of type 2 diabetes. The drug is the fourth dipeptidyl peptidase-4 inhibitor after sitagliptin (Januvia), saxagliptin (Onglyza), and linagliptin (Tradjenta). Takeda Pharmaceuticals has been seeking approval for more than 5 years, dealing with the FDA's tighter standards for new diabetes drugs. The approval was based on 14 trials involving about 8500 patients as well as five ongoing postmarketing trials. The agency also approved two additional combinations of alogliptin with metformin and pioglitazone. Alogliptin alone will be marketed as Nesina, alogliptin/metformin will be marketed as Kazano, and alogliptin/pioglitazone will be marketed as Oseni. Both combination products carry boxed warnings (for lactic acidosis associated with metformin and heart failure associated with pioglitazone). All three are distributed by Takeda Pharmaceuticals.

Johnson & Johnson is one step closer to approval of canagliflozin, the first of a new type of diabetes drug. The Endocrionologic and Metabolic Drugs Advisory Committee voted 10 to 5 in favor of approving the drug while still expressing some concern about the cardiovascular safety of the agent. Canagliflozin is an oral inhibitor of the sodium glucose cotransporter 2 (SGLT2) that reduces reabsorption of glucose in the kidney, resulting in increased urinary glucose excretion with a consequent lowering of plasma glucose levels as well as weight loss. If eventually approved by the FDA, it would be the first SGLT2 inhibitor on the U.S. market. The FDA denied a similar drug 1 year ago (dapagliflozin) because of increased risk of bladder and breast cancer. The favorable vote was based on clinical trials of more than 10,000 patients worldwide which showed that the drug improves blood sugar levels and led to modest weight loss as well as reduction in blood pressure. ■