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Hospital Medicine

Evidence-Based Information for Hospitalists Intensivists, and Acute Care Physicians [ALERT]

Vol. 8, Issue 1, March 2013
www.ahcmedia.com

ABSTRACT & COMMENTARY

Using Low-Dose Aspirin to Prevent Recurrent Venous Thromboembolism

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationships relevant to this field of study.

This article originally appeared in the Jan. 15, 2013, issue of Internal Medicine Alert. *It was edited by Stephen Brunton, MD, and peer reviewed by Gerald Roberts, MD. Dr. Brunton is Adjunct Clinical Professor, University of North Carolina, Chapel Hill, and Dr. Roberts is Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, New York, NY. Dr. Brunton serves on the advisory board for Abbott, Boehringer Ingelheim, Janssen, Novo Nordisk, Sanofi, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Kowa, Novo Nordisk, and Teva. Dr. Roberts reports no financial relationship to this field of study.*

SYNOPSIS: Aspirin therapy, as compared with placebo, significantly reduced the rate of major vascular events with improved net clinical benefit and also reduced the rate of recurrent venous thromboembolism.

SOURCE: Brighton TA, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med* 2012;367: 1979-1987.

It is well known that patients who have had an episode of unprovoked venous thromboembolism are at high risk for recurrence after anticoagulant therapy is discontinued.[1-2] Long-term warfarin anticoagulant therapy has proven to be very effective in preventing a recurrence of venous thromboembolism, but is associated with an increased risk of bleeding and is inconvenient from the patient's point of view.[3-6] As a result, many patients will discontinue their warfarin therapy after 3-6 months despite recommendations for prolonged therapy.[5]

Brighton and his colleagues evaluated the

Financial Disclosure: *Hospital Medicine Alert*'s physician editor, Kenneth P. Steinberg, MD, executive editor Russ Underwood, and associate managing editor Jill Drachenberg have no relevant financial relationship related to the material presented in this issue.

Hospital Medicine [ALERT]

Hospital Medicine Alert, ISSN 1931-9037, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305. Website: www.ahcmedia.com.

EXECUTIVE EDITOR:
Russ Underwood.

GST Registration Number: R128870672. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to Hospital Medicine Alert, P.O. Box 105109, Atlanta, GA 30348.

Back Issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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efficacy of low-dose aspirin compared to placebo in preventing a recurrence of venous thromboembolism in patients who had completed initial anticoagulation therapy with warfarin after a first unprovoked episode of venous thromboembolism. They performed the Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) study,[7] which was a double-blind, randomized, placebo-controlled study of 822 patients who had completed initial anticoagulation therapy with heparin followed by warfarin or another effective anticoagulant therapy after the first episode of unprovoked venous thromboembolism. A target INR of 2.0-3.0 was recommended while on warfarin therapy that was maintained for 6 to 12 months. Subjects were randomly assigned to receive a 100 mg dose of aspirin or placebo. The patients on aspirin demonstrated a large, although not significant, reduction in the rate of recurrence of venous thromboembolism. Most importantly, the patients also demonstrated a significant reduction in the rate of occurrence of other major vascular events, including myocardial infarction, stroke, or cardiovascular death.

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Although the results of the trial performed by Brighton et al did not demonstrate a significant reduction in the primary outcome of recurrent venous thromboembolism with aspirin as compared to placebo therapy in patients who had suffered a first unprovoked venous thromboembolic incident and had been treated with 6-12 months of warfarin therapy, they did demonstrate that aspirin therapy significantly reduced the secondary composite outcome of major vascular events by 34% without increased bleeding. With fewer patients recruited than originally planned, the trial by itself was not sufficiently powered to show a significant reduction in the primary outcome, but when combined with the WARFASA study[8] results, in which patients had baseline characteristics that were similar, a clear effect was evident. The combined results of the two trials revealed a highly significant reduction of 32% in the rate of recurrent venous thromboembolism and a reduction of 34% in the rate of major vascular events with no excess bleeding.

It is well known that the risk of late reoccurrence of venous thromboembolism after a first unprovoked event remains high at approximately 10% in the first year.[1,2] Therefore, it is important to have an alternative form of medical therapy for the many patients who are unwilling to accept extended warfarin therapy because of its inconvenience and the increased risk of developing significant bleeding. Although aspirin is less effective than warfarin, this study by Brighton et al suggests that aspirin therapy is an attractive alternative to warfarin because it is simple, inexpensive, and has a well-documented safety profile. Aspirin has now been demonstrated to be effective by producing a significant overall reduction in the risk of major thrombotic events and cardiovascular death and a large, although not statistically significant, reduction in the rate of recurrent venous thromboembolism.

In summary, low-dose aspirin therapy appears to be beneficial in preventing recurrent venous thromboembolism and major vascular events in patients who had a first episode of unprovoked venous thromboembolism. It also appears to be an attractive therapeutic option for these patients after they have completed an initial course of warfarin therapy. ■

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ABSTRACT & COMMENTARY

Time Spent in Handoff Discussions was Longer for Patients Discussed First, Regardless of Complexity

By Leslie A. Hoffman, RN, PhD
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Leslie A. Hoffman reports no financial relationships relevant to this field of study.
This article originally appeared in the February 2013 issue of Critical Care Alert. *It was edited by David J. Pierson, MD, and peer reviewed by William Thompson, MD. Dr. Pierson is Professor Emeritus, Pulmonary and Critical Care Medicine, University of Washington, Seattle, and Dr. Thompson is Associate Professor of Medicine, University of Washington, Seattle. Drs. Pierson and Thompson report no financial relationships relevant to this field of study.*

SYNOPSIS: Disproportionately longer time was allocated to ICU patients discussed early in attending physician handoff sessions, regardless of complexity or severity of illness.

SOURCE: Cohen MD, et al. The earlier the longer: Disproportionate time allocated to patients discussed early in attending physician handoff sessions. *Arch Intern Med* 2012;172:1762-1764.

Handoffs have been extensively examined as a potential source of communication failure. Such studies typically focus on how to best share details of care when patient responsibility is transferred from one clinical care team to another. In contrast, this study analyzed the handoff process in regard to the order of discussion and, in particular, time spent discussing individual patients. Video recordings were made of 23 end-of-week handoff sessions in a 21-bed ICU located in a tertiary medical center. The ICU was staffed by two teams, each led by an outgoing attending physician who handed off to an incoming attending. The procedure followed in this unit was to discuss patients in "bed-list" order. With frequent admissions and discharges, the discussion of patients was therefore effectively randomized, making severity of illness or other patient characteristics unrelated to discussion order. For the 262 sessions recorded, mean session duration was 142 ± 98 seconds. The average time allocated to each patient declined steadily from the first to last patient discussed. First-discussed patients received about 50% more time than those discussed last in a handoff session.

■ COMMENTARY

This article presents an interesting perspective regarding the content of handoff sessions. Time spent discussing patients "first on the list" was disproportionately longer than that spent discussing those later in the session, regardless of acuity, complexity, time of admission, or other factors. To confirm findings, the authors used three statistical approaches, all of which produced highly similar estimates. Through patient handoffs, responsibility, authority, and information about patients are exchanged between care providers. If incomplete or quickly verbalized, the information shared can impact the quality of patient care, predispose patients to unnecessary procedures/tests, and increase risk of adverse events.

A recent systematic review identified 18 articles

analyzing characteristics of handoffs conducted in hospital settings.[1] Studies identified in this review analyzed outcomes regarding a wide range of factors believed to influence subsequent care: use or non-use of a handoff sheet/mnemonic to standardize topics discussed, team behavior, clinician characteristics, patient characteristics, etc. None of these articles included consideration of "place in line." Findings of this study suggest a simple-to-implement, no-cost solution that can improve the transfer of information during handoffs, i.e., discussing the most complex, most unstable, or new admissions first and/or setting blocks of time for return to cases that require further discussion. ■

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ABSTRACT & COMMENTARY

Apixaban vs Warfarin for Atrial Fibrillation

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. *It was peer reviewed by Ethan Weiss, MD, Assistant Professor of Medicine, Division of Cardiology and CVRI, University of California, San Francisco. Dr. Crawford reports no financial relationships relevant to this field of study, and Dr. Weiss is a scientific advisory board member for Bionovo.*

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 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. ■

ABSTRACT & COMMENTARY

Are You Feeling the Heat of Professional Burnout? You Are Probably in Good Company!

By Jeff Unger, MD
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Dr. Unger reports no financial relationships relevant to this field of study.
This article originally appeared in the Jan. 29, 2013, issue of Internal Medicine Alert. *It was edited by Stephen Brunton, MD, and peer reviewed by Gerald Roberts, MD. Dr. Brunton is Adjunct Clinical Professor, University of North Carolina, Chapel Hill, and Dr. Roberts is Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, New York, NY. Dr. Brunton serves on the advisory board for Abbott, Boehringer Ingelheim, Janssen, Novo Nordisk, Sanofi, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Kowa, Novo Nordisk, and Teva. Dr. Roberts reports no financial relationship to this field of study.*

SYNOPSIS: A total of 27,276 U.S. physicians received an invitation to participate in a prospective study using the validated Maslach Burnout Inventory. Of the 26% of physicians who completed the survey, nearly 46% reported at least one symptom associated with professional burnout. Family physicians, internists, neurologists, and emergency department physicians appeared to be at highest risk for burnout. This study found that 37.9% of all physicians were likely to have symptoms of burnout compared with 27.8% of non-medical working adults.

SOURCE: Shanafelt TD, et al. Burnout and satisfaction with work-life balance among US physicians relative to the general US population. *Arch Intern Med* 2012;172:1377-1385.

This was the first national study that evaluated and compared rates of burnout among U.S. clinicians by specialty with non-physician U.S. workers. Table 1 summarizes the most notable conclusions of this study.

■ COMMENTARY

Few primary care physicians (PCPs) believe that this trend is likely to be reversed in the near future. Having 21 million patients deposited on our doorsteps as the result of the Affordable Health Care Act is likely to result in loss of autonomy, reduction in compensation, increased federal regulations, and higher medical-legal exposure. Patients are likely to become more demanding of a medical system that will be unable and unwilling to provide timely interventions to those in need. More pressure will be placed on PCPs to provide efficient, evidence-based care to patients with chronic illnesses. Unfortunately, even the most intelligent and organized clinicians will be hard pressed to provide care for a new patient with diabetes during a single 10-minute office appointment! With all of the demands that are placed on each of us, especially solo practitioners, I am surprised that not more of our colleagues are experiencing burnout. Remember our first day on the job? The first patient you ever saw professionally? The first baby you ever delivered? The first life you ever saved? The first real diagnosis you ever made? The first hand you held of a dying patient? The first time you ever sutured a wound or assisted in surgery? How exciting and memorable were those experiences? Remember the first pay check you received as a "real doctor?" My father received a check for $15 as a resident working at Cook County Hospital back in 1950. Back then, they did *not* pay the interns who were expected to work 80 hours a week. My dad said he cannot remember any of

Table 1

U.S. Physician Burnout Talking Points

- Burnout rate among U.S. physicians is 45.4%.
- Higher rates of burnout were observed among family physicians, general internists, neurologists, and emergency medicine specialists.
- Of all respondents to the survey, 37.8% appeared to have clinical depression (based on evaluation of data attained from the Primary Care Evaluation of Mental Disorders screening instrument).
- With nearly 50% of clinicians experiencing "burnout" and one-third depressed, the trend toward dysfunction is alarming.

his fellow interns ever experiencing burnout. The residents who earned $15 per week did not experience burnout or depression either. They were simply excited about being doctors.

Now, times are so very different. My father had to retire from the practice of medicine this year at age 85. He could have worked longer, but he said, "it isn't worth it anymore." There are so many more regulations and busy work that we must do on a daily basis that we are lucky to get home before 9 p.m. When the doors to the office are finally closed and the staff is discharged, the practitioner or his designated associate must enter data related to meaningful use, PQRS, and other performance parameters into the computer. Failure to e-prescribe, maintain board certification, and supply Medicare with these parameters will result in financial penalties further reducing per-patient compensation. In 2013, the Centers for Medicaid & Medicare Services (CMS) estimates that the statutory formula used to determine Medicare physician payments will result in a decrease of 27%![1]

Burnout in any profession occurs when one's job becomes overwhelming or if one is unable to control his/her own destiny. Physicians work long hours and are forced to spend inadequate time with complex patients. Patient-centered medical homes may offer PCPs the option of seeing fewer patients on a daily basis in an efficiently organized practice that may be income generating.[2,3]

I believe that the major triggers for physician burnout in the United States are: 1) the CMS; 2) private insurers who base compensation on CMS recommendations; 3) government regulations that increase health care costs and reduce treatment efficiency; and 4) increased taxes on small businesses that result in our inability to hire new personnel, purchase new equipment, or even take time off to enjoy a week or two with our family. Until working conditions and compensation for frontline specialists improve, more of us will burnout and suffer from major depression. ■

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ABSTRACT & COMMENTARY

Surgeon-To-Patient HBV Transmission, CDC Update on Chronically Infected

By Stan Deresinski, MD, FACP, FIDSA

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This article originally appeared in the February 2013 issue of Infectious Disease Alert. *It was peer reviewed by Timothy Jenkins, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford University, and Dr. Jenkins is Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Deresinski does research for the National Institutes of Health, and is an advisory board member and consultant for Merck, and Dr. Jenkins reports no financial relationships relevant to this field of study.*

SOURCE: Enfield KB, et al. Transmission of hepatitis B virus from an orthopedic surgeon with a high viral load. *Clin Infect Dis* 2013;56:218-24.

A surgeon reported having suffered a sharps injury while performing an orthopedic procedure. Baseline testing found no evidence of HBV infection in the source patient, but determined that the surgeon had preexisting HBV infection, with positive HBsAg, positive HBeAg, negative IgM anti-HBc, and normal serum hepatic transaminases. The surgeon had emigrated from a country with a high prevalence of HBV infection, had completed his residency training in the U.S., and had been employed at a different hospital prior to his current place of practice. He had previously received 2 complete courses of HBV vaccination without developing a protective level of anti-HBs. However, no additional testing of HBV markers had been performed at that time.

Because his serum HBV DNA concentration was >17.9 million IU/mL, he was removed from surgical practice. Former patients of the surgeon at his previous facility were evaluated for evidence of HBV infection. Of the 232 patients who consented to testing, 2 had acute HBV infection and their virus had >99.9% nucleotide identity with that of the surgeon. There were an additional 6 patients who had evidence of past HBV exposure without other identified risk factors, suggesting possible transmission from the surgeon. Two patients had evidence of past HBV exposure but had risk factors; transmission from the surgeon was considered indeterminate in these cases. The surgeon was considered to be technically proficient and no breaches in procedure were retrospectively identified.

■ COMMENTARY

It is useful to examine the management of the surgeon described by Enfield and colleagues relative to current guidelines.[1,2] The Centers for Disease Control and Prevention now recommends that providers and students at increased risk for HBV infection, such as, in this case, those born to mothers in or from endemic countries, should undergo prevaccination testing. Prevaccination testing for chronic HBV infection should also be performed on all providers performing exposure-prone procedures. Health-care providers who do not have a protective concentration of anti-HBs (>10 mIU/ml) after revaccination (i.e., after receiving a total of 6 doses) should be tested for HBsAg and anti-HBc to determine their infection status. This was not done with the surgeon described.

HBV infection in health-care providers and students who do not perform invasive exposure-prone procedures should be managed as a personal health issue and does not require special oversight. In contrast, chronically infected surgeons and others who perform exposure-prone Category I activities should undergo oversight by an Expert Panel. CDC has defined 2 categories of exposure-prone patient care procedures (confusingly, SHEA has 3 categories, with a reverse order of risk and with an intermediate Category II defined as one in which procedures for which transmission is theoretically possible but unlikely):

Category I. Procedures known or likely to pose an increased risk of percutaneous injury to a health-care provider that have resulted in provider-to-patient transmission of HBV. These procedures are limited to major abdominal, cardiothoracic, and orthopedic surgery, repair of major traumatic injuries, abdominal and vaginal hysterectomy, caesarean section, vaginal deliveries, and major oral or maxillofacial surgery (e.g., fracture reductions). Techniques that have been demonstrated to increase the risk for health-care provider percutaneous injury and provider-to-patient blood exposure include:

- digital palpation of a needle tip in a body cavity and/or
- the simultaneous presence of a health care provider's fingers and a needle or other sharp instrument or object (e.g., bone spicule) in a poorly visualized or highly confined anatomic site.

Category II. All other invasive and noninvasive procedures.

CDC recommends that HBV infection alone should not disqualify infected individuals from the study or practice of surgery, dentistry, medicine, or allied health fields, but strongly emphasizes the need for strict adherence to standard precautions. They also recommend against a variety of potentially onerous monitoring and management requirements as well as constraints on practice. Chronically infected surgeons and others who perform Category I activities may conduct such procedures if low or undetectable HBV viral load is documented at least every 6 months, or more frequently as indicated by such factors as a change in antiviral therapy. A threshold viral load level of 1000 IU/ml (5000 genome equivalents/ml) is recommended, as is an assay with a lower limit of detection of 10-30 IU/ml. Fluctuations above the threshold will necessitate that the provider abstain from performing exposure-prone procedures while subsequent retesting occurs, and if

needed, modifications or additions to the health-care provider's drug therapy and other reasonable steps are taken.

Finally, the Consult Subcommittee of CDC's Public Health Ethics Committee has noted that providers have an ethical and professional obligation to know their HBV status and to act on such knowledge accordingly.

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CME QUESTIONS

1. In the randomized, controlled trial by Brighton et al., that enrolled patients after completion of initial anticoagulant therapy for unproved venous thromboembolism, aspirin compared to placebo was associated with:

a. A large but statistically insignificant decrease in recurrence of venous thromboembolism.
b. A significant decrease in the rate of occurrence of other major vascular events.
c. A significant decrease in the rate of cardiovascular mortality.
d. All of the above.

2. In the observational study by Cohen and colleagues, when attending physicians signed out ICU patients during their weekly hand-offs, they:

a. Discussed the sickest patients first.
b. Spent the most amount of time discussing the patients with a DNAR status.
c. Spent the most amount of time discussing the first patients on the list regardless of severity.
d. Used only written sign-out materials and did not discuss any of the patients.

3. In a secondary analysis of the ARISTOTLE trial by Hohnlosser and collaborators, patients with atrial fibrillation and reduced renal function treated with apixaban instead of warfarin had:

a. Fewer strokes and a reduction in major bleeding complications.
b. Fewer strokes but an increase in major bleeding complications.
c. No difference in stroke but a reduction in major bleeding complications.
d. No difference in stroke and an increase in major bleeding complications.

CME OBJECTIVES

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

- discuss pertinent safety, infection control and quality improvement practices;
- explain diagnosis and treatment of acute illness in the hospital setting; and;
- discuss current data on diagnostic and therapeutic modalities for common inpatient problems.

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VOLUME 18, NUMBER 3 PAGES 5-6 MARCH 2013

When One Antihypertensive Med is Not Enough: Which Combination?

Source: Kato J, et al. *J Am Soc Hypertens* 2012;6:393-398.

THE ALLHAT TRIAL IS THE LARGEST HYPERtension clinical trial ever done, originally enrolling more than 42,000 individuals. That trial concluded that a thiazide diuretic (chlorthalidone) was at least as good as — and in some situations superior to — a calcium channel blocker ([CCB] amlodipine) or an angiotensin converting enzyme inhibitor ([ACE] lisinopril), and that an alpha blocker (doxazosin) was inferior to any of the three others.

But ALLHAT also demonstrated that only about 25% of hypertensives are able to maintain control on one medication. So, when one antihypertensive med is not enough, which combination should we choose?

The ACCOMPLISH trial was the first to address this question on a large-scale basis (n = 11,506) by directly comparing ACE/CCB (benazepril/amlodipine) with ACE/diuretic (benazepril/hydrochlorothiazide). In this trial, outcomes were superior for ACE/CCB.

Not everyone can tolerate an ACE, most commonly due to cough. Kato et al performed a clinical trial to compare in 58 hypertensive elderly patients (mean age, 72 years) the efficacy of an angiotensin receptor blocker (ARB)/CCB (mostly olmesartan/amlodipine) with ARB/diuretic (mostly olmesartan/indapamide).

At the conclusion of the trial, the ARB/CCB combination provided superior blood pressure reduction to ARB/diuretic. The diuretic used in ALLHAT was chlorthalidone, which is definitely more potent than hydrochlorothiazide; whether substitution of chlorthalidone for indapamide in this trial might have tipped the scales in another direction remains unknown. ■

Vitamin D for Osteoarthritis: NOT

Source: McAlindon T, et al. *JAMA* 2013; 309:155-162.

FOR A BURGEONING POPULATION OF BABYboomers who wish to continue being physically active despite advanced years, tools to provide symptomatic relief from osteoarthritis (OA) are valuable (e.g., topical and systemic NSAIDs, opioids, physical therapy), but disease-modification is really the "holy grail." At the current time, we do not possess any disease-modifying pharmacotherapy for OA.

Since vitamin D (VID) is an important player in bone health, might it influence symptoms or disease progression of OA? McAlindon et al performed a 2-year randomized, placebo-controlled trial of VID in subjects with symptomatic OA of the knee. VID dose was titrated from 2000 IU/d up to as much as 8000 IU/d, depending on attainment of a goal plasma VID level between 36-100 ng/mL. In this population of mostly Caucasian adults (mean age, 62 years) living in the Boston area, it is perhaps not surprising that baseline levels of VID averaged 22 ng/mL.

At the end of the trial, no effect (positive or negative) was seen from supplementation with VID on either OA symptoms or evidence of disease progression as measured by degree of cartilage loss. ■

Early Identification of COPD Exacerbations

Source: Yanez AM, et al. *Chest* 2012; 142:1524-1529.

ACUTE EXACERBATIONS OF CHRONIC OBstructive pulmonary disease (AECOPD) are consequential: 10% of patients admitted to the hospital die, 25% of those admitted to the ICU die, and the mortality rate in the year following an AE-COPD hospitalization for those who are discharged home is as high as 43%. Even after successful recovery from an AE-COPD, decrements in pulmonary function from pre-event status are noted that are not regained. Early identification of AE-COPD, with an intent-to-treat with minimum delay, might possibly alter the ominous natural history of AE-COPD.

Historically, it has been shown that the increasing dyspnea characteristic of AECOPD typically begins about 5 days before patients seek consultation from their clinician. For asthma, wider swings in variation between morning and evening peak flow rate herald an acute deterioration, even before patients are overtly symptomatic. In a similar vein of thought, the authors postulated that changes in respiratory rate would signal an impending AE-COPD.

Oxygen-dependent COPD patients (n = 89) were asked to monitor respiratory rate daily for 3 months. Monitoring of daily respiratory rate (DRR) was performed automatically by installing a monitoring device to the patients' oxygen delivery systems. Although respiratory rate was monitored at three different times each day, only the mean DRR rate was used for evaluation.

During 3 months of follow-up, 30 of

the 89 patients required hospitalization for AE-COPD. Baseline average DRR for the group as a whole was 16 breaths/minute; among the subgroup ultimately admitted for AE-COPD, baseline DRR was 15.2. In the 5 days prior to an AE-COPD admission, their DRR increased to 19.1, but no meaningful change in DRR was seen in patients not requiring hospital admission. DRR may provide a new window into early identification of AE-COPD. ■

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. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media.

Executive Editor: Leslie Coplin.
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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. ■