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INSIDE

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Is 'Silent' Atrial Fibrillation in Diabetics Associated with Cerebral Neurologic Events?

ABSTRACT & COMMENTARY

By Edward P. Gerstenfeld, MD

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Dr. Gerstenfeld does research for Biosense Webster, Medtronic, and Rhythmia Medical. This article originally appeared in the October 2013 issue of Clinical Cardiology Alert.

Synopsis: *The authors concluded that subclinical AF episodes are common in diabetics and predict a higher incidence of subsequent cerebral ischemic events.*

Source: Marfella R, et al. Brief episodes of silent atrial fibrillation predict clinical vascular brain disease in type 2 diabetic patients. *J Am Coll Cardiol* 2013;62:525-530.

Patients with diabetes have twice the stroke risk of those without diabetes. Yet, only 15% of diabetic patients have symptomatic atrial fibrillation (AF). This study sought to address the question of whether there was a relationship between asymptomatic AF and cerebral events in type 2 diabetics with no evidence of AF or stroke.

The study included two phases: 1) a 4-year recruitment period to enroll patients from a cohort of 1992 type 2 diabetic patients and 2) a 3-year follow-up period. Patients included in the follow-up arm had to meet the following criteria: age < 60 years, successful completion of quarterly 48-hour Holter monitors during the screening phase, and completion of brain magnetic resonance imaging (MRI). Patients with any baseline history of AF, stroke, transient ischemic attack (TIA), or structural heart disease were excluded. Four hundred sixty-four patients were enrolled and compared to 240 healthy subjects without diabetes or any of the exclusion criteria. During the screening phase, patients underwent 48-hour Holter monitors every 3 months with silent AF classified as any episode lasting at least 10 minutes and < 48 hours in duration. Patients were then classified into either a group with silent AF (SAFE group, n = 176) or a group without silent AF (non-SAFE group, n = 288). All patients were

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treated with aspirin 75-325 mg daily, and if CHADS2 score was > 1, oral anticoagulation with warfarin was initiated. Patients were then followed for 36 months for the occurrence of any clinical neurologic events. The incidence of "silent" AF was much higher among diabetic patients compared to healthy controls (11% vs 1.6%; $P < 0.001$). The mean AF burden was 21 ± 15 hours in the SAFE group compared to 3 ± 1.4 hours in the healthy control group ($P < 0.001$). On MRI, a subclinical thromboembolic ischemic event (SCI) was detected more often in the SAFE group compared to the non-SAFE group (61% vs 29%; $P < 0.01$). The AF burden was correlated to the size and number of SCI events. Using multivariate analysis, silent AF, left atrial size, systolic blood pressure, and duration of diabetes were independently associated with SCI. During the 36-month follow-up, clinical AF episodes occurred in 15% of patients who were excluded from the analysis; 26 patients (15%) in the SAFE group and and 19 patients (7%) in the non-SAFE group were treated with warfarin anticoagulation. Despite this, a clinical ischemic stroke developed in more patients in the SAFE compared to the non-SAFE groups (17.3% vs 5.9%; $P < 0.01$). No strokes occurred in the healthy control group. Of the 43 stroke events, 42 were ischemic and one was hemorrhagic. The authors concluded that subclinical AF episodes are common in diabetics and predict a higher incidence of subsequent cerebral ischemic events.

■ COMMENTARY

Patients with type 2 diabetes have a higher incidence of cerebrovascular events and AF compared to those without diabetes. However, there has not been a definitive link established between the two. Diabetes is also associated with hypercoaguability and vascular endothelial dysfunction that could play a role in SCIs. This ambitious study carried out over 7 years has several important findings. First, the prevalence of silent AF in a population of type 2 diabetics is approximately 10% higher than previously reported. Second, patients with diabetes and silent AF have a very high incidence of SCI on MRI examination (61%). Finally, patients with diabetes and silent AF, even episodes lasting < 48 hours, have a high incidence of strokes during follow-up (17.3%). This should be an eye-opener for physicians following patients with diabetes mellitus.

Should we screen our patients with type 2 diabetes for silent AF? It is difficult to know if the patients in the centers enrolling for this study were subject to a referral bias that increased their thromboembolic risk. However, I think the data demonstrating a 10% prevalence of asymptomatic AF and strong association with both silent and overt clinical neurologic events support screening of high-risk diabetic patients for asymptomatic AF. Obviously the cost-effectiveness of this approach has not been established, nor has the efficacy of treating diabetic patients with asymptomatic AF with systemic anticoagulation. While this study was performed before the era of the newer oral anticoagulants, the advent of the oral direct thrombin and factor X inhibitors have certainly lowered the threshold for initiating systemic anticoagulation in AF patients at risk of stroke. One could certainly envision a multicenter, randomized trial screening diabetic patients for brief episodes of asymptomatic AF, and then randomizing them to aspirin or anticoagulation with a novel anticoagulant. However, until more data become available, it certainly is reasonable to have a low threshold to initiate anticoagulation in diabetic patients who have a clinical neurologic event, and to have increased vigilance screening of diabetic patients with multiple AF risk factors for silent AF. We await more data on this important topic. ■

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Two-step Screening for Ovarian Cancer: A 'Scissor-step' Forward?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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Dr. Coleman reports no financial relationships relevant to this field of study. This article originally appeared in the October 2013 issue of OB/GYN Clinical Alert.

Synopsis: *An 11-year prospective screening trial in 4051 menopausal women (age 50-74) demonstrates that the risk of ovarian cancer algorithm probability index, along with ultrasound and gynecologic oncology consultation of "high-risk" cases, produces high specificity and positive predictive value leading to the identification of higher than expected incident early-stage ovarian cancers.*

Source: Lu KH, et al. A 2-stage ovarian cancer screening strategy using the risk of ovarian cancer algorithm (ROCA) identifies early-stage incident cancers and demonstrates high positive predictive value. *Cancer* 2013; Aug 26. Doi: 10.1002/cncr.28183 [Epub ahead of print].

Ovarian cancer is a highly lethal disease of low prevalence in the general population and is associated with advanced stage presentation in more than 70% of incident diagnoses. Strategies to identify these clinical features early in the disease process have included a focus on symptomatology, blood-based biomarkers, imaging (predominately ultrasonography), and physical exam with little success.

In this study, a two-stage ovarian cancer screening strategy was evaluated that incorporates change of CA125 levels over time and age to estimate risk of ovarian cancer. Women with high-risk scores were referred for transvaginal ultrasound (TVS). The prospective study included postmenopausal women (age 50-74) with at least one retained ovary, no personal history of ovarian cancer, and no family history of a first- or second-degree relative with breast or ovarian cancer. Patients were excluded if they had had another malignancy, other than breast cancer, within 5 years of enrollment. Participants underwent an annual CA125 blood test. Based on the Risk of Ovarian Cancer Algorithm (ROCA) result, women were triaged to a subsequent annual CA125 test if deemed low risk, a repeat CA125 test in 3 months if intermediate risk, or TVS and referral to a gynecologic oncologist if high risk. A total of 4051 eligible women participated over 11 years, accounting for 16,832 screen years. The average annual rate of referral to a CA125 test in 3 months was 5.8%, and the average annual referral rate to TVS and review by a gynecologic oncologist was 0.9%. Ten women underwent surgery on the basis of TVS triage, which identified four invasive ovarian cancers (one with stage IA disease, two with stage IC disease, and one with stage IIB disease), two ovarian tumors of low malignant potential (both stage IA), one endometrial cancer (stage I), and three benign ovarian tumors, providing a positive predictive value of 40% (95% confidence interval [CI], 12.2%, 73.8%) for detecting invasive ovarian cancer. The specificity was 99.9% (95% CI, 99.7%, 100%). All four women with invasive ovarian cancer were enrolled in the study for at least 3 years with low-risk annual CA125 test values prior to rising CA125 levels (CA125 change point). The authors concluded that ROCA followed by TVS demonstrated excellent specificity and positive predictive value in a population of U.S. women at average risk for ovarian cancer.

■ COMMENTARY

Some may recall the children's game "Mother may I?" in which participants follow instructions from a leader (mother) trying to guess the progress of the participants (children) toward a goal (home). Granted requests, such as "baby steps" or "scissor steps," afford minor advancements toward progress. The current study, while offering hope and promise of bridging the gap between early detection and mortality from ovarian cancer, essentially represents a minor, albeit positive, step forward. It clearly demonstrates that the process will involve several key elements such as good biomarkers, good probability estimate algorithms, motivated follow-up, access to secondary triage and gynecologic oncology consultation, and ultimately validation by documentation of reduction in mortality. However, to reach this zenith, studies assessing the merits of the individual steps forward are necessary and build confidence in the process.

It is clear that a screening program's best opportunity to reduce disease mortality is to identify a pre-invasive state where intervention will prevent disease.[1] Currently, we have no such marker for ovarian cancer, which likely also consists of a high proportion of fallopian tube abnormalities that form the primary site of disease.[2] Thus, the next best opportunity to affect mortality in ovarian cancer is "stage migration;" that is, diagnosing the disease at earlier stages than what is currently observed in the general population. This can measurably impact survival as early-stage disease is curable at rates two- to three-fold that of advanced disease. Since more than 70% of ovarian cancer diagnosed in 2013 is stage IIIC/IV, there is significant opportunity to vastly alter its natural history and expected disease-specific mortality under a screening program that results in significant stage migration. The performance of the two-step screening algorithm used in this trial is remarkably consistent with the initial prevalence report presented by the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)[3] group in 2009.[4] Although incidence was not reported in that study, the general specificity and positive predictive value of the two-step algorithm (which is similar to the current study) were very consistent and, fortunately for screening participants, required only two to three operations from "positive screens" to identify cases of ovarian cancer — all in "early-ish" stages (Stage IC-IIB).

It was also of interest that two of the four cancers identified in this study had "normal" CA-125 values but met

the criteria for a significant CA125 change point while remaining within the normal range. This highlights the value of establishing a normal baseline and the power of serial investigation. In addition, nearly 85% of all participants just went on getting annual CA-125 tests, demonstrating the low overall specificity of the program. The 200,000 person UKCTOCS trial's primary endpoint is disease-specific mortality; it is hoped that the preliminary results will be confirmed, offering practice changing policies in the management of screening menopausal women. ■

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Hypertension in the Elderly May Be Associated with Progressive Brain Atrophy

ABSTRACT & COMMENTARY

By Michael T. Lin, MD

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Dr. Lin reports no financial relationships relevant to this field of study. This article originally appeared in the October 2013 issue of Neurology Alert.

Synopsis: *Mid-life hypertension may be a risk factor for late-life brain atrophy and may exacerbate neurodegeneration. However, lowering blood pressure too aggressively in those with advanced atherosclerotic vascular disease may also result in late-life brain atrophy.*

Source: Jochemsen HM, et al. Blood pressure and progression of brain atrophy: The SMART-MR study. *JAMA Neurol* 2013;70:1046-1053.

Hypertension is well established as a risk factor for vascular brain lesions. There is also emerging evidence that abnormal blood pressure may be a risk factor for neurodegeneration. Several cross-sectional studies have shown that high blood pressure in midlife is associated with more brain atrophy later in life, whereas in late life, low blood pressure is associated with more brain atrophy. However, there is little prospective evidence relating blood pressure and brain atrophy.

The SMART-MR (Secondary Manifestations of ARTerial disease-Magnetic Resonance) study in the Netherlands is a prospective, cohort study of MRI brain changes in patients with arterial disease — coronary artery disease, cerebrovascular disease, peripheral artery disease, or abdominal aortic aneurysm. Of 1309 patients enrolled from 2001-2005, 663 had MRIs at baseline and during follow-up from 2006-2009. Average follow-up time was 3.9 years, average age was 57, and 81% were men. The ventricular fraction was used as a measure of subcortical brain atrophy, and the ventricular fraction increased with time in all blood pressure groups.

The key findings were 1) that in those with low diastolic blood pressure (DBP) at baseline, the increase in ventricular fraction was greater than in those with high DBP at baseline (this finding was driven primarily by patients with coronary artery disease); and 2) in those with normal or high DBP at baseline, the increase in ventricular fraction was less if DBP decreased over time than if it increased. Findings were adjusted for demographic factors, other vascular risk factors, alcohol consumption, baseline brain volume, and baseline burden of strokes and white matter lesions.

Of note, previous studies found that low blood pressure was associated with increased brain atrophy in late life, whereas this study observed low DBP to be associated with increased brain atrophy in mid-life in patients with arterial disease. The authors hypothesized that patients with arterial disease have early vascular aging with increased arterial stiffness, impaired endothelial function, and impaired cerebral autoregulation, making them more vulnerable to low blood pressure. Because this association of low blood pressure and increased brain atrophy occurred primarily in patients with coronary artery disease, baseline low DBP might represent poor cardiac output and insufficient brain perfusion. On the other hand, in those with higher DBP at baseline, the association of decline in blood pressure over time with less brain atrophy suggests that treating abnormally high blood pressure will be beneficial.

■ COMMENTARY

Strengths of this study include its prospective design and large numbers of patients. The poor follow-up rate is

a weakness, and it is not clear whether these findings will generalize to patients without arterial disease. Nonetheless, many patients do have arterial disease, and this study further emphasizes the emerging understanding of how vascular risk factors are related to neurodegeneration as well as stroke. Practically, the study suggests that blood pressure should be treated in patients with hypertension, but should not be lowered further in patients who already have normal or low blood pressure, particularly in the setting of an acute intercurrent illness. ■

Infectious Disease Malpractice: The $1.2 Million Miscommunication

By Joseph Patterson, MD, Cyril Fider, MD, and Gregory Moore, MD

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Infectious diseases account for a significant percentage of emergency department (ED) visits each year and are frequent sources of litigation. A plaintiff verdict or settlement is usually based on a delay in diagnosis and subsequent substandard treatment. It is important to recognize specific infectious entities early to avoid medical-legal exposure.

In Anonymous Woman v. Anonymous Physician and Anonymous Nurse, a 40-year-old female was referred from her primary care physician to the ED after presenting with 5 days of headache, fever, and body aches. An initial evaluation consisting of a lumbar puncture, urinalysis, and blood cultures was performed, and she was discharged with blood cultures pending after the other tests were negative. Two days later, the blood cultures grew group B streptococcus. A nurse was instructed to call the patient back, but was unsuccessful after two attempts at the home number on different days — no attempt was made to contact the primary care doctor who referred the patient. The physician stated that the nurse was instructed to call the patient back for treatment, while the nurse stated that the culture results were thought to be a contaminant and the call was meant to see how the patient was doing. The patient returned 6 days after the initial visit with worsening symptoms and was admitted for treatment of endocarditis. The patient was also found to have aortic regurgitation and valvular disease, expected to require a valve replacement. The defense claimed that the damage was pre-existing and not worsened by the delay in diagnosis and treatment, but a $1.2 million settlement was reached.[1]

Infective endocarditis is an inflammation of the lining of the heart or its valves with an infectious agent, usually bacteria. Diagnosis is challenging, and untreated disease is associated with significant complications and a mortality rate approaching 100%.[2] The above case illustrates two excellent points. The first concerns follow-up. The follow-up call was delegated to a nurse, and the physician and nurse gave conflicting statements on the purpose of the calls. Additionally, the primary care doctor was not contacted as another means of reaching the patient. In the end, the patient was never reached with the results and it would be difficult to say that every effort had been made to contact the patient.

There are a plethora of cases in which blood culture results were inadequately communicated. These cases universally result in court settlements or payouts. It is imperative that the ED have a follow-up protocol that is 100% compliant. Interestingly, the defense argument was that the damage was already done, not that the delay was the patient's fault for not giving a reliable phone number or checking her messages.

The second point is that infective endocarditis bears special consideration as a diagnosis that is both difficult to make and dangerous to miss. Patients typically present with vague constitutional symptoms and fevers. The median age of onset is 67, although this can occur at much younger ages based on other comorbidities or IV drug abuse,[3] and the median time from symptom onset to diagnosis is 8 days.[4]

Diagnosis has been standardized with the Duke criteria, which are quoted at approximately 90% sensitivity. They consist of two major and six minor criteria. The major criteria are positive blood cultures (the presence of typical bacteria from two separate blood cultures or in persistently positive blood cultures) and evidence of echocardiographic involvement. The minor criteria are a predisposition to the disease, fever (> 38° C), vascular phenomena, immunologic phenomena, suggestive echocardiogram, and suggestive microbiologic findings.[5] In 2000, these criteria were modified to drop suggestive echocardiogram findings as a minor criterion and divide cases into one of three categories — definite infective endocarditis (two major criteria; one major and three minor; or five minor), possible (one major and one minor; or three minor), or rejected (due to a firm alternative diagnosis, resolution of the syndrome with ≤ 4 days of antibiotics, no pathologic

evidence on autopsy or surgery, or not meeting the criteria above).[6]

While most of the criteria are self evident, one deserves additional discussion. Predisposition to the disease is anything that allows bacteria to accumulate on the endocardium and is generally due to an anatomic valvular defect, causing turbulent flow that injures the endothelium, a foreign object such as a mechanical valve, or injection drug use. A thorough history or review of records can provide one of the criteria, along with raising the clinician's index of suspicion. Along with the formal diagnostic criteria, lab findings of anemia, hematuria, and elevated ESR, CRP, or procalcitonin have been identified as being strongly associated with the disease but nonspecific.[2]

As noted above, patients are at risk of significant morbidity and mortality if the disease is not identified and treated with a prolonged course of antibiotics. Along with the ill effects of prolonged bacteremia, the disease process can result in direct damage to the heart or valves, with heart failure or arrhythmias as a result. Additionally, fragments of the bacteria and clot that cling to the heart valve can break off and embolize, causing infarction or abscess in any area of the body, including the lungs, the mesentery, the eyes, and the brain, with the most common CNS complication being a middle cerebral artery embolic stroke.[2,3] These devastating complications can be minimized or avoided with admission for IV antibiotics as well as early surgical removal of the bacterial vegetation in higher-risk cases. ■

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Pharmacology Update

Hydrocodone Bitartrate Extended-Release Capsules (Zohydro™ ER)

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

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

The FDA has approved the first single-entity, extended-release hydrocodone product for the treatment of chronic pain. It will be a Schedule II controlled substance and part of the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS). It is manufactured by Zogenix and marketed as Zohydro ER.

Indications

Hydrocodone ER capsules are indicated for the management of pain that requires daily, around-the-clock, long-term opioid treatment in patients in which alternative opioids are not adequate.[1]

Dosage

For opioid-naïve and opioid-intolerant patients, the starting dose is 10 mg every 12 hours.[1] The dose may be increased at increments of 10 mg every 12 hours every 3-7 days. Other opioids may be converted to hydrocodone ER with a conversion factor. The dose should be titrated individually based on analgesic effect and tolerability. Capsules are available as 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg.

Potential Advantages

With the single entity, the dose of hydrocodone is not limited by dose limitations of acetaminophen.

Potential Disadvantages

This extended-release product may be targeted for diversion since it is not formulated to be abuse deterrent. In the worst case scenario, the drug could potentially be crushed and snorted or dissolved and injected.[1] The FDA is requiring postmarketing studies to assess safety as well as risk of misuse and abuse.[2] Many in the FDA lobbied for an abuse deterrent form of the product (similar to Purdue Pharmaceutical's Oxycontin), but the agency decided

against such restrictions.

Comments

The efficacy and safety of hydrocodone ER capsules were evaluated in a placebo-controlled study in opioid-experienced subjects with moderate-to-severe pain due to low back pain.[1] Subjects entered an open-label conversion and titration phase where they were converted from their pre-study opioid and titrated to an effective dose (up to 6 weeks). Subjects (n = 302) were then randomized at a 1:1 ratio to a titrated, fixed dose of hydrocodone ER (maximum of 200 mg/day) or matching placebo for 12 weeks. The latter group went through a blinded-taper. Subjects were allowed to use hydrocodone 5 mg/acetaminophen 500 mg as rescue medication (up to 2 doses per day). At 12 weeks, 67.5% had at least 30% improvement in pain from baseline compared to 31.1% for placebo. Eighty-two percent (82%) of subjects in the hydrocodone arm completed the 12-week study compared to 39% for the placebo arm. The most common adverse events were constipation and nausea.

Clinical Implications

Hydrocodone ER offers another long-acting option for the treatment of chronic pain. The FDA recommends that hydrocodone ER be reserved for patients who are not adequately managed or cannot tolerate alternative analgesics. Hydrocodone is addictive and its short-acting forms (Vicodin, Norco, Lortabs) have frequently been the target of abuse and diversion. The lack of an abuse-deterrent with this formulation may increase the risk of misuse, abuse, and overdose as well as theft and diversion. The cost was not available at the time of this review. ■

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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 Instructions

To earn credit for this activity, follow these instructions:

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3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
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5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter! ■

CME Questions

1. Subclinical atrial fibrillation events detected on ambulatory ECG monitoring are:
   a. associated with strokes.
   b. common in normal subjects.
   c. frequent in diabetes.
   d. a and c

2. Which of the following characteristics was a stated eligibility or exclusion of women in the ovarian cancer screening trial?
   a. Age > 50 years
   b. At least one intact ovary
   c. Previous history of ovarian cancer
   d. No evidence of another cancer within 5 years of initial screening

3. Hypertension affects the brain in all of the following *except*:
   a. risk factor for ischemic stroke.
   b. risk factor for hemorrhagic stroke.
   c. may induce an acute encephalopathy.
   d. improves cerebral perfusion.

Clinical Briefs

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

Dr. Kuritzky is a retained consultant for Boehringer Ingelheim, Daiichi Sankyo, Forest Pharmaceuticals, Janssen, Lilly, Novo Nordisk, Pfizer, and Sanofi.

Long-Term Risk-Reduction Benefits of Sigmoidoscopy and Colonoscopy

Source: Nishihara R, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med* 2013;369:1095-1105.

Participants from two large observational studies provide an opportunity to evaluate the risk reduction accrued from either colonoscopy (COL) or sigmoidoscopy (SIG). The Nurses' Health Study (n = 121,700 female nurses) and the Health Professionals Follow-up Study (n = 51,529 male health professionals) have more than 20 years' prospective follow-up of their participants. During this interval, there were 1185 cases of colon cancer and 474 deaths from colon cancer.

Skeptics have long held fast to the tenet that SIG had an advantage over COL: proven risk reduction for colon cancer mortality for the former. Although the intuitive additional advantage of examining the entire colon with COL seemed a no-brainer, purists argued that whether COL was truly better than SIG was not yet proven, and that since COL was associated with greater risks (perforation, adverse effects from sedation, etc.), there was reasonable basis to continue with SIG as a preferred method. In accord with this philosophy, noting the many missed opportunities for colon cancer screening and prevention, advocacy groups rallied around the call-to-action, "The best colon cancer screening test is whichever one you can get done!"

These data may change that perspective, since the risk reduction for colon cancer death was almost twice as great for COL as SIG (hazard ratios, 0.59 vs 0.32). The "no-brainer" part of the equation was also resoundingly confirmed: COL reduced mortality from proximal colon cancer by more than half compared to no risk reduction through SIG. ■

Consequences of Non-Adherence in Treated Hypertensives

Source: Cummings DM, et al. Medication adherence and stroke/TIA risk in treated hypertensives: Results from the REGARDS study. *J Am Soc Hypertens* 2013;7:363-369.

The relationship between elevated blood pressure (BP) and stroke is linear and continuous. An abundance of clinical trial data indicate that treatment of hypertension (HTN) by means of numerous diverse classes of antihypertensives lowers stroke risk by ≥ 40%. Clinical trials, however, are not "real life." The Reasons for Geographic and Racial Disparities in Stroke (REGARDS) study is examining a large population (n = 30,239) of southeastern men and women with HTN. Their assessment of the relationship between self-reported degree of antihypertensive medication adherence and serious outcomes (stroke/TIA) from a subset population (n = 15,071) is quite sobering.

During a 5-year window of observation, study participants were grouped into four categories of adherence using the Morisky scale, which translates into general groupings of high, good, moderate, and low adherence. Perhaps not surprisingly, mean systolic BP in the high adherence group was substantially better than the low adherence group (131 mmHg vs 138 mmHg). Incidence of stroke or TIA was 8% higher in the lowest adherence group compared to the highest. Good BP control has meaningful payoff; every decrement of adherence less than that is costly. ■

Warfarin Outperforms Dabigatran in Patients with Mechanical Heart Valves

Source: Eikelboom JW, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013;369:1206-1214.

The atrial fibrillation (AF) headlines have been filled with celebration over the efficacy of factor Xa inhibitors (e.g., rivaroxaban, apixaban) and direct thrombin inhibitors (e.g., dabigatran) for prevention of thrombotic events. Since warfarin — though highly effective, exhaustively studied, and time-tested — also has distinct clinical burdens (e.g., need for monitoring, food interactions, drug interactions), agents that were at least as efficacious for thrombotic risk reduction — with fewer of these same clinical burdens — were welcomed.

Success in AF, however, does not necessarily translate into other pathologies. Eikelboom et al studied patients with recent mitral or aortic mechanical valve replacement (n = 252). Subjects were randomized to dabigatran or warfarin. About one-fourth of these patients also had AF.

The trial had to be discontinued early because of untoward events in the dabigatran group: stroke occurred in 5% of the dabigatran group vs none in the warfarin group, and major bleeding was twice as common on dabigatran (4% vs 2%). Although earlier trials in animals were encouraging, these data indicate that warfarin is safer and better tolerated in patients with recent surgery for prosthetic mechanical heart valves. ■

In Future Issues: More Good News About the Mediterranean Diet!