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Replacing Warfarin for Atrial Fibrillation Treatment — A Foregone Conclusion!

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

Clinical Assistant Professor, West Virginia University School of Medicine, Charleston, WV

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

Synopsis: *In nonvalvular atrial fibrillation patients, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. However, an intention-to-treat analysis did not show superiority of rivaroxaban over warfarin.*

Source: Patel MR, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-891.

RIVAROXABAN (XARELTO) IS A DIRECT FACTOR XA INHIBITOR THAT MAY BE a potentially attractive alternative to vitamin K antagonists. For the outpatient treatment and prevention of venous and arterial thromboembolic conditions, oral vitamin K antagonists such as warfarin are commonly recommended by clinicians. Atrial fibrillation (AF) is a common but serious cardiac rhythm disturbance and is responsible for substantial morbidity and mortality in the general population. AF is an independent risk factor for mortality and is associated with a doubling of mortality in both sexes. The most serious complication of AF is stroke, the risk of which is increased 4-5 fold in people with existing AF.[1] In patients with AF, the estimated risk of stroke without anticoagulation therapy is 5% per year. However, pooled data from five randomized, controlled trials demonstrated that warfarin use reduces the risk of stroke by approximately 68%.[2] Due to its narrow therapeutic range, warfarin poses significant challenges as well as the need for frequent monitoring, multiple drug and food interactions, and the risk of bleeding. In patients with AF, for the prevention of stroke, warfarin dosage is typically adjusted to achieve a target International

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Normalized Ratio (INR) of 2 to 3. An INR less than 1.8 doubles the risk of stroke, whereas an INR greater than 3.5 does not further benefit patients but increases the risk of bleeding. Rivaroxaban can potentially provide more consistent and predictable anticoagulation as a once-daily dosing option, which requires no therapeutic monitoring, and has a lower potential for drug interactions. In previous trials, rivaroxaban has been shown to be superior to enoxaparin in prevention of total deep venous thrombosis, and noninferior to enoxaparin followed by warfarin in a study of patients with deep venous thrombosis.[3]

In the study referred commonly to as the ROCKET AF trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), the researchers used a double-blind design to randomly assign 14,264 patients with nonvalvular AF who were at moderate-to-high risk for stroke to either once-daily oral rivaroxaban or dose-adjusted warfarin (INR = 2.5). This multicenter, randomized, double-dummy, multinational trial was conducted at 1178 sites from December 2006 through May 2010 and supported by Johnson & Johnson and Bayer. The primary hypothesis was that rivaroxaban would be noninferior to warfarin for the prevention of stroke or systemic embolism. An analysis termed "per-protocol, as treated" was designed to determine this noninferiority. The primary efficacy endpoint was the composite of stroke (ischemic or hemorrhagic) and systemic embolism. Approximately 23.7% in the rivaroxaban group and 22.2% in the warfarin group permanently stopped their assigned therapy before an endpoint event and before the termination date. The median duration of treatment exposure was 590 days; the median follow-up period was 707 days, and only 32 patients were lost to follow-up. In patients included in the primary efficacy analysis, the primary endpoint (stroke or systemic embolism) occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 in the warfarin group (2.2% per year) (hazard ratio in the rivaroxaban group, 0.79; 95% confidence interval [CI], 0.66 to 0.96; $P < 0.001$ for noninferiority). In the intention-to-treat analysis, the primary endpoint occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year; hazard ratio, 0.88; 95% CI, 0.74 to 1.03; $P < 0.001$ for noninferiority; $P = 0.12$ for superiority). In essence, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism in patients with AF. However, an intention-to-treat analysis did not show the superiority of rivaroxaban over warfarin. Additionally, there was no significant difference in the risk of major bleeding between the two groups, although intracranial and fatal bleeding was statistically less in the rivaroxaban group.

■ COMMENTARY

Whether rivaroxaban (Xarelto) is at least as good as (noninferior) warfarin for preventing stroke or systemic embolism in patients with AF could depend on how one interprets these data. Noninferiority trials are intended to demonstrate that the effect of a new treatment is not worse than that of an active control by more than a specified margin. In noninferiority trials, the "constancy assumption" must be satisfied: the new trial must be designed in a way similar to the past trials so that the control treatment, as administered in the new trial, must have the same magnitude of benefit relative to placebo as it had in the reference trials. There are significant concerns about the above study meeting this constancy assumption, and therefore it has led many to doubt the authors' claim of meeting the noninferiority assessment in ROCKET-AF. Furthermore, in the intention-to-treat superiority analysis, investigators failed to show that rivaroxaban had an advantage, statistically, over warfarin for the prevention of thromboembolic events in patients with nonvalvular AF. A striking increase in death rates after the discontinuation of randomized treatment further complicates the noninferiority assessment in ROCKET-AF. Recently, the FDA's Cardiovascular and Renal Drug Committee recommended approving rivaroxaban for the prevention of stroke and systemic embolism in nonvalvular AF patients. Due to its simplicity of use, rivaroxaban may become a useful alternative in patients who have an inadequate response to or cannot be prescribed dabigatran or warfarin. However, we will still need a significant amount of postmarketing data to demonstrate efficacy and safety, including methods on

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rapidly reversing the anticoagulation in patients with life-threatening hemorrhages. ■

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Brief Report

Strokes More Severe When Occurring During Sleep

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College, New York, NY

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

This article originally appeared in the October issue of Neurology Alert. *At that time it was peer reviewed by M. Flint Beal, MD, Anne Parrish Titzel Professor, Department of Neurology and Neuroscience, Weill Cornell Medical Center, New York, NY. Dr. Beal reports no financial relationships relevant to this field of study.*

Source: Kim BJ, et al. Ischemic stroke during sleep: Its association with worse early functional outcome. *Stroke* 2011; 42:1901-1906.

IT HAS BEEN WELL RECOGNIZED THAT A PEAK IN STROKE ONSET occurs during the early morning hours. This possible circadian periodicity is not well understood, and may in part represent stroke onset earlier during the night that goes unrecognized until the patient arouses. "Wake up stroke" (WUS) presents a challenge to treatment, since time of onset has been strictly defined as the last time the patient was seen normal, and therefore these patients fail to be candidates for thrombolytic treatment. Recently, some investigators have suggested that a subset of WUS patients could be thrombolysis candidates, especially if imaging could be suggestive of a shorter time of onset.

In the current study, Kim et al compare outcomes among 2289 patients retrospectively reviewed, with 637 (27.8%) of these being WUS. Three separate analytic techniques were used. In a dichotomized analysis, with patients split into a functionally independent group (modified Rankin score 0-1) or functionally dependent group (Rankin > 2); there was no difference between WUS and non-WUS. However, when stroke severity was taken into account, WUS patients fell into a more unfavorable category more frequently (odds ratio [OR] 1.33). Additionally, when the Rankin score was used as a continuous variable, patients with WUS consistently trended toward being more dependent at discharge (OR 1.22).

Patients with WUS had a higher proportion of strokes attributed to large vessel atherosclerotic disease, which is not unexpected given their increased severity. Also, not surprisingly, patients with WUS were less likely to be treated with intravenous thrombolysis, though a subset did receive endovascular interventions.

■ COMMENTARY

As the investigators note, adverse outcomes for WUS patients may be due to more than merely delay in presentation and lack of thrombolytic therapy. Hemodynamic changes during sleep, especially autonomic shifts during early morning rapid eye movement sleep, may act as stroke precipitants. An increase in platelet aggregation also has been shown to peak during this time period, which has been thought to contribute to a circadian variability in myocardial infarction, sudden cardiac death, and stroke. Sleep-disordered breathing also may be a factor due to associated hypoxia, hypertension, or cardiac arrhythmias. Of note, body mass index (a known risk factor for obstructive sleep apnea) was not different between WUS and non-WUS patients. Sleep apnea is nevertheless a well-recognized risk factor for stroke and needs to be investigated and treated among patients at risk. ■

A Better Understanding of Nocturia in Patients with Interstitial Cystitis

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

Clinical Professor, Department of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville, TN

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

This article originally appeared in the October issue of OB/GYN Clinical Alert. *At that time it was peer reviewed by Catherine Leclair, MD, Associate Professor, Department of OB/GYN, Oregon Health & Science University Portland, OR. Dr. Leclair reports no financial relationships relevant to this field of study.*

Synopsis: *Both urgency and bladder pain can lead to nocturia in patients with interstitial cystitis.*

Source: Warren JW, et al. Nocturia in insterstitial cystitis/painful bladder syndrome. *Urology* 2011;77:1308-1312.

In this case-control study, a well-established database of patients with interstitial cystitis/painful bladder syndrome (IC/PBS) was used to identify women with nocturia. The authors studied information from two data sets: a) baseline and follow-up interviews and b) self-administered questionnaire. Nocturia was associated with both urgency and bladder pain to varying degrees. Both symptoms also were perceived by the subjects to be the reason for awakening. For many patients, bladder pain either directly awakened them or indirectly caused awakening by triggering a sensation of urgency to void.

■ COMMENTARY

The various subtleties involved with this topic are fascinating … at least they are to me. Taking the history is one thing, and then trying to figure out the significance of those symptoms and events is another. When I see patients referred to me for chronic pelvic pain, dyspareunia, or voiding problems, it surprises me to find many who have never been questioned about and/or treated for nocturia. Based on what we know about IC/PBS, the history of nocturia is a significant finding, so the presumed take-home message is that we should ask about this symptom routinely.

Similarly, appreciating a tender bladder on physical examination is an important aspect of determining the source of pain. This requires a conscientious and inquisitive provider who is able to differentiate the bladder from other anatomic components (e.g., pelvic floor muscles, uterus, adnexa) as the potential source of pelvic pain. The authors help us to realize that nocturia is actually a process that includes the stimulation to awake (the subject of this study), the actual awakening, getting up from the bed, going to the bathroom, and then urinating. We are reminded that patients sometimes awaken for reasons unrelated to pain or the urge to void (e.g., noise), but use that occasion to void.

Useful for the practicing women's health provider is the knowledge that the literature tells us that nocturia is associated with diabetes, restless legs syndrome, snoring, depression, and coronary artery disease. The symptom of nocturia has four general causes: sleep disorders, reduced bladder capacity, nocturnal polyuria, and global polyuria. Pain generally is not correlated with nocturia in the general population. In contrast, since pain is the hallmark of IC/PBS, it behooves us to think of patients with the symptom of nocturia as something potentially indicative of IC/PBS.

So the next time you have a patient with chronic pelvic pain, don't forget to ask about nocturia, because it will remind you about IC/PBS as a possible diagnosis. Similarly, even if the patient doesn't specifically mention nocturia, the physical examination finding of a tender bladder might lead you to a diagnosis missed by others. ■

ACE Inhibitors/ARBs for Aortic Stenosis?

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco, CA

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

This article originally appeared in the October issue of Clinical Cardiology Alert. *At that time it was peer reviewed by Ethan Weiss, MD, Associate Professor of Medicine, Division of Cardiology, University of California, San Francisco, CA. Dr. Weiss is an advisory board member for Bionovo.*

Synopsis: *The authors conclude that this large observational study suggests ACEI or ARB therapy is associated with an improved survival and a lower risk of cardiovascular events in patients with aortic stenosis.*

Source: Nadir MA, et al. Impact of renin-angiotensin system blockade therapy on outcome in aortic stenosis. *J Am Coll Cardiol* 2011;58:570-576.

In severe symptomatic aortic stenosis (AS), surgical AVR improves mortality, but there is no medical therapy proven to slow progression of the valvular stenosis. Because AS is accompanied by left ventricular (LV) hypertrophy and fibrosis, and because the risk factors for AS are similar to those for coronary artery disease (CAD), it makes sense that blockade of the renin-angiotensin system may benefit patients with AS. Nadir and colleagues performed a retrospective observational study to address this issue. They linked several databases in the Tayside region of Scotland and were able to ascertain patient level data, including echocardiographic data, mortality, hospital admissions, medications, and laboratory tests. The use of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in patients with AS identified by echocardiography was then studied in terms of clinical outcomes.

A total of 2117 patients with AS were identified, 46% were male and the mean age was 73 ± 12 years. Aortic stenosis was mild or moderate in 75%, and severe in 25%. One-third of patients were on ACEI or ARB thera-

py. There were significant baseline differences between those who received ACEIs or ARBs and those who did not receive them. Those receiving ACEIs or ARBs were older, and had a higher prevalence of LV dysfunction, diabetes, and prior cardiovascular (CV) events. However, they had less severe AS and more of them were receiving aspirin, beta-blockers, digoxin, anti-coagulants, and statins.

After a mean follow-up of 4.2 years, patients taking ACEIs or ARBs had lower mortality and fewer cardiovascular (CV) events. Adjusted hazard ratio (HR) for death was 0.76 ($P < 0.0001$) and for CV events was 0.77 ($P < 0.0001$). When stratified by severity of AS, the use of ACEI or ARB therapy was associated with a greater reduction in CV events in patients with severe AS (HR 0.64, $P = 0.04$) than in mild or moderate AS (HR 0.78, $P = 0.01$). To confirm these findings, the authors performed a propensity score matched cohort analysis on 532 patients. In this analysis, they also found that the use of ACEI or ARB therapy was associated with a reduction in all-cause mortality (HR 0.67) and CV events (HR 0.71). They also performed a time-scale analysis (Kaplan Meier) that confirmed these results. Importantly, for those patients in whom on-treatment blood pressure recordings were available (330 patients), there was no difference in systolic or diastolic blood pressure between groups. The authors conclude that this large observational study suggests ACEI or ARB therapy is associated with an improved survival and a lower risk of CV events in patients with AS.

■ COMMENTARY

Arterial vasodilators have long been relatively contraindicated in patients with severe LV outflow obstruction. Several medications, including ACEIs, have failed to prevent progression of AS severity in clinical trials. This dataset from Nadir and colleagues is intriguing because they did not study the severity of the valve disease, but instead chose to study clinical events in AS patients. They demonstrate a striking reduction in CV events and death in patients taking ACEIs or ARBs, and this reduction in CV events was greater in those with more severe AS. The mechanism of the benefit is not immediately clear. It may relate to protection against myocardial fibrosis and hypertrophy, which are arrhythmogenic substrates. Alternatively, it may reduce vascular events, such as myocardial infarction. It is important to recognize that there were significant differences in baseline characteristics between groups. The authors performed several different statistical analyses that all demonstrated similar findings, which increases the confidence in their results. Despite this rigorous statistical methodology, there are likely to be confounding factors for which their analyses could not account. Therefore, it is important to interpret the data cautiously. However, their data do suggest that ACEIs or ARBs are safe in AS.

In light of these data, should all patients with AS be treated with ACEIs or ARBs? I think it is too soon to make such recommendations. However, if another indication for such a therapy exists, such as concomitant hypertension, then ACEIs or ARBs would be a reasonable choice for an antihypertensive. Future studies into the mechanism of any potential benefit, as well as prospective, randomized, controlled clinical trials are needed before we can recommend ACEIs or ARBs in patients with AS. ■

Pharmacology Update

Vemurafenib Tablets (Zelboraf™)

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

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

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

A KINASE INHIBITOR FOR LATE-STAGE MELANOMA AND ITS companion diagnostic test have been approved by the FDA. Vemurafenib is specifically for patients with melanoma whose tumor expresses a gene mutation called BRAF V600E. It is the second drug approved for late-stage melanomas after the monoclonal antibody, ipilimumab (Yervoy™). Vemurafenib was reviewed under the FDA's priority review program. The drug is marketed by Genentech as Zelboraf™.

Indications

Vemurafenib is indicated for the treatment of unresectable or metastatic melanoma with BRAF mutation as detected by the FDA-approved test (cobas® 4800 BRAF V600 Mutation Test).

Dosage

The recommended dose is 960 mg (4x 240 mg) taken orally twice daily.[1] The tablets should be swallowed whole with or without a meal. Dose reduction, interruption, or discontinuation may be required if adverse reactions occur, however dose reduction below 480 mg twice daily is not recommended.

Vemurafenib is available as 240 mg tablets.

Potential Advantages

Vemurafenib has been shown to improve overall and progression-free survival compared to dacarbazine in patients with mutation positive metastatic melanoma.[1,2]

Potential Disadvantages

Common adverse events (30% or higher) include arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, and skin papilloma.[1] Cutaneous squamous cell carcinoma and keratoacanthomas have been reported. These tend to occur with a median time of 7 to 8 weeks of therapy and approximately one-third of patients experienced more than one occurrence. Close to 40% of patients required dose modification due to adverse effects.[2] Vemurafenib is not recommended in patients with uncorrectable electrolyte abnormalities or long QT syndrome, or for those who are on drugs that may prolong QT interval.[1] The drug is a moderate inhibitor of CYP1A2, a weak inhibitor of CYP2D6, and an inducer of CYP3A4. Concomitant use with substrates with narrow therapeutic windows for these isoenzymes is not recommended.[1]

Comments

Vemurafenib is a potent inhibitor of some mutated forms of BRAF, particularly BRAFT V600E. The efficacy and safety of vemurafenib was shown in a Phase 3 randomized trial comparing it with dacarbazine (n = 675).[1,2] Patients with unresectable, previously untreated stage IIIC, or stage IV melanoma and positive for BRAF V600 mutation were randomized to vemurafenib (960 mg twice daily) or dacarbazine (1000 mg/m^2 intravenously on day 1 every 3 weeks). The efficacy endpoints were overall survival, investigator-assessed progression-free survival, and confirmed investigator-assessed best overall response rate. After a median follow-up of 6.2 months in the vemurafenib group (n = 337) and 4.5 months in the dacarbazine group (n = 338), the number of deaths were 23% and 36%, respectively (hazard ratio [95% CI] 0.44 [0.33,0.59]; $P < 0.0001$). The hazard ratio for progression-free survival was 0.26 (0.20, 0.33). The confirmed investigator-assessed best overall response rate was 48.4% with vemurafenib compared to 5.5% for dacarbazine.[3] Responses were partial as there were two complete responses in the vemurafenib group and none in the dacarbazine group. Seventy-five percent of responses occurred by month 1.6 of treatment. Adverse event related dose modification or interruption occurred in 38% of patients on vemurafenib compared to 16% for dacarbazine. Cutaneous squamous cell carcinoma, keratoacanthoma, or both occurred in 18% of vemurafenib-treated patients.[2] Some evidence of acquired clinical resistance to vemurafenib has been reported.[4]

Clinical Implications

Late-stage melanoma carries a poor prognosis and is the leading cause of death from skin disease with median survival ranging from 8 to 18 months.[5] BRAF V600E mutation is found in 50% to 60% of melanoma. Vemurafenib represents an important treatment for this disease in patients with the BRAF mutation. Earlier this year, the FDA approved ipilimumab that also has been shown to improve survival in patients with this disease with previously treated unresectable or metastatic melanoma. ■

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PS Form **3526,** October 1999 *(Reverse)*

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:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
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. **When compared to warfarin, using rivaroxaban (Xarelto) for the prevention of stroke or systemic embolism in patients with nonvalvular atrial fibrillation was found to be:**
   a. noninferior.
   b. superior.
   c. inferior.
   d. noninferior or superior.

2. **ACEI/ARB treatment for aortic stenosis patients:**
   a. is contraindicated.
   b. reduces mortality.
   c. reduces CV events.
   d. b and c

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

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

Long-Term Azithromycin for Prophylaxis of COPD Exacerbations

Source: Albert RK, et al. *N Engl J Med* 2011;365:689-698.

For many patients with moderate-severe chronic obstructive pulmonary disease, acute exacerbations (AECOPD) are highly problematic. For hospitalized AECOPD, the mortality rate is approximately 10%; loss of pulmonary function that typically accompanies an AECOPD is usually not regained; mortality during the year following an AECOPD is increased. Hence, reduction and/or delay of AECOPD is an important goal.

Macrolides are often the antimicrobial agents chosen to treat AECOPD. This trial in patients with COPD randomized subjects to azithromycin 250 mg qd (n = 570) or placebo (n = 572) for 1 year. The patient's background COPD treatments were unchanged. The primary outcome of the trial was time to first AECOPD. Secondary outcomes included QOL, and scores on the St. Georges Respiratory Questionnaire. More than three-fourths of study participants were receiving background inhaled steroids, long-acting beta agonists, and/or long-acting anticholinergics during the trial.

Azithromycin prophylaxis was associated with a statistically significant prolongation of time to first AECOPD, as well as a 27% relative-risk reduction in the frequency of AECOPD. The St. George's Respiratory Questionnaire scores were improved significantly more in the azithromycin group. One adverse effect analyzed was affect on hearing function: Azithromycin was associated with a slightly higher incidence of hearing decrement than placebo. However, improvements in hearing noted on follow-up occurred whether the drug was discontinued, suggesting that perhaps the incidence of hearing decrements were initially overestimated.

Azithromycin prophylaxis may provide important benefits in COPD, especially for persons with frequent AECOPD. ■

Unintended Medication Consequences of Hospital Admission

Source: Bell CM, et al. *JAMA* 2011; 306:840-847.

Most hospitalizations have a focused agenda: heart failure, pneumonia, acute trauma, etc. It is not at all difficult to conceive that as a consequence of intensified focus on one or more often acute problems, attention can be drawn away from the issues of lesser acuity, such as maintenance medications for dyslipidemia, dysglycemia, or thyroid disease. Sometimes because of discontinuity between persons involved in the patient's hospitalization and outpatient providers, inadvertent discontinuation of necessary chronic medications can be overlooked.

Using the database of patients in Ontario, Canada (n = 396,380; age 66 and older), Bell et al examined prescription data to see whether chronic medications from five different classes experienced discontinuation subsequent to hospitalization. The five classes were: statins, antiplatelet/anticoagulants, levothyroxine, respiratory inhalers, and gastric acid inhibitors.

Hospitalization was associated with an increased incidence of discontinuation of all five classes of agents. Hospitalization, which included ICU admission, was disproportionately likely to be associated with chronic medication discontinuation. Equally distressing, the data demonstrated an increased risk for death or subsequent hospitalization in persons who discontinued their chronic medications. Gaps in continuity of care are of significant consequence to hospitalized patients. ■

Is Mercury Really a Bad Guy in CV Disease?

Source: Houston MC. *J Clin Hypertens* 2011;13:621-627.

Mercury has a bad rap sheet: it decreases cellular oxidative defenses, increases oxidative stress, reduces the effectiveness of metalloenzymes, induces mitochondrial dysfunction, increases vascular inflammation, and worsens endothelial function. In addition, mercury toxicity is associated with increased carotid intima-media thickness. Omega-3 fatty acids, as contained in fish, can antagonize some of the detrimental effects of mercury. However, fish in the diet are also currently the major source of human exposure to mercury.

There is no known biologic or physiologic role of mercury in the body, hence it must be regarded as a toxin.

Observational data generally, but inconsistently, find an association between tissue levels of mercury and cardiovascular disease. For hypertension particularly, numerous different populations have found a relationship between tissue mercury levels and blood pressure (systolic, diastolic, and pulse pressure). Chronic mercury toxicity may be inexpensively measured by a 24-hour urine mercury level. The author does not include mention of any trials indicating favorable effects achieved by modulation of mercury, although selenium, by complexing with mercury, may mollify some of its toxic effects. ■

In Future Issues: Chocolate Consumption and Cardiometabolic Disorders