AHC Media

Vol. 30, Issue 10, October 2011
www.ahcmedia.com

Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

Risk of Cardiac Events After Surgery

By Michael H. Crawford, MD, Editor

SOURCES: Gupta PK, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. *Circulation* 2011;124:381-387. Grover FL, Edwards FH. Objective assessment of cardiac risk for noncardiac surgical patients: An up-to-date simplified approach. *Circulation* 2011;124:376-377.

Perioperative cardiac events are the leading cause of surgical mortality. Thus, there has been considerable interest in predicting which patients are at highest risk. However, current risk prediction schemes have significant limitations. Thus, Gupta and colleagues analyzed the American College of Surgery National Surgery Quality Improvement Program database to determine factors associated with perioperative myocardial infarction (MI) or cardiac arrest, and to develop a risk calculator. Data from 2007 through 2008 were collected from about 200 hospitals in the United States. The 2007 data on more than 200,000 surgeries were used as the derivation set and the 2008 data (also > 200,000 surgeries) were used for validation. Only trauma patients, transplant patients, and those patients younger than 16 years old were excluded.

The database included patients with aortic (2.1% of population), cardiac (0.3%), and peripheral arterial surgery (8.3%). Perioperative MI or cardiac arrest was seen in 0.65% of the validation group. Multivariate logistic regression analysis identified five significant predictors of MI or cardiac arrest: type of surgery, functional status, elevated creatinine, American Society of Anesthesiology class, and older age. In the validation set, a risk calculator based on these five factors had an area under the receiver operating curve (AUC) of 0.87, compared to the Revised Cardiac Risk Index (RCRI) of 0.75. In those patients undergoing aortic or noncardiac vascular surgery, the AUC was 0.75 vs the RCRI value of 0.59. The authors concluded that their cardiac risk calculator surpasses the performance of the RCRI and should simplify the informed consent process.

Financial Disclosure: *Clinical Cardiology Alert's* Editor, Michael H. Crawford, MD, reports no financial relationships relevant to this field of study, and peer reviewer, Ethan Weiss, MD, is a scientific advisory board member for Bionovo. Managing Editor, Neill Kimball, and Executive Editor, Leslie Coplin, report no financial relationships relevant to this field of study.

Clinical Cardiology [ALERT]

Clinical Cardiology Alert, ISSN 0741-4218, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road., NE Building 6, Suite 400 Atlanta, GA 30305.

POSTMASTER: Send address changes to *Clinical Cardiology Alert*, P.O. Box 105109, Atlanta, GA 30348.

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■ COMMENTARY

This paper has elevated the bar on cardiac event risk prediction in patients undergoing surgery of all types, but especially non-cardiovascular surgery. Notably, it uses a computer-based direct logarithmic regression model to determine the risk of MI or cardiac arrest like the STS or Euro-score do for cardiac surgery, rather than a point score system like the RCRI and most older schema (i.e., Goldman, Detzky). You can access the calculator at www.surgicalriskcalculator.com/miorcardiacarrest. The data entry is very simple and involves only five variables. 1. the American Society of Anesthesiology class (1-5): normal healthy patient (1), mild systemic disease, severe systemic disease, severe plus life threatening and moribund (5). 2. functional class as independent or partially or fully dependent (0 or 1); 3. creatinine > 1.5 (0, 1); 4. type of surgery classified as high risk (aortic, brain, hepatobiliary) or moderate (all others); and 5. age as a continuous variable.

One strength of this new schema is that it was derived from > 200,000 patients as compared to > 4000 for the RCRI and it performed better. Also, it includes newer laparoscopic surgeries and it is organ based. In addition, it has better discriminatory power, especially for vascular surgery, as compared to the RCRI.

There are limitations to the surgical risk calculator. The major ones for cardiology consultations are the lack of inclusion of information on stress test results, echocardiogram results, history or evidence of arrhythmias, beta-blocker use, and prior revascularization. These data may significantly alter risk, especially in the patient with known or suspected coronary artery disease. The definition of MI, especially in cardiac surgery patients, is problematic. In this study, they chose three times the upper limit of a normal troponin to exclude demand induced events. This is reasonable, but may be a strength or a weakness depending on your point of view.

I believe this is a significant step forward in this area and believe this new schema should replace the RCRI, especially for most patients undergoing non-cardiovascular surgery. It could be a starting point for evaluating patients undergoing cardiovascular surgery or those with known vascular disease, but other information will need to be considered in these patients before making a final decision on the risk of surgery. Unfortunately this study did not shed any light on the use of preoperative beta-blockers or stress tests, which remain controversial. The editorial by Grover and Edwards emphasizes that risk calculators are only one part of clinical decision making and are definitely not the whole enchilada. They believe this type of objective data will help with patient and family discussions, and consultations with other providers. In conclusion, we now have a better risk predictor tool, but the cardiology consultation has not been replaced by a computer yet. ■

ABSTRACT & COMMENTARY

New Oral Anticoagulant for Atrial Fibrillation

By John P. DiMarco, MD, PhD
Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

Dr. DiMarco does research for Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific.

SOURCE: Granger CB, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-992.

This report is from the ARISTOTLE trial, which was just reported at the recent European Society of Cardiology meeting in Paris. Apixaban is a new direct oral factor Xa inhibitor with a favorable pharmacokinetic profile.

This study compared apixaban to adjusted-dose warfarin in patients with nonvalvular atrial fibrillation. The trial had a double-blind, double-dummy trial design. Patients were randomly assigned to treatment with either apixaban or adjusted-dose warfarin. The primary objective was to compare apixaban to warfarin for reducing the risk of ischemic or hemorrhagic stroke or systemic embolism in atrial fibrillation patients. The primary safety outcome was major bleeding.

Patients were eligible for enrollment if they had documented atrial fibrillation and one or more risk factors for stroke. Patients with mitral valve disease, prosthetic heart valves, recent strokes, any need for continuous high-dose antiplatelet therapy, and moderate to severe renal insufficiency were excluded. Patients with a prior history of warfarin therapy were eligible but randomization was stratified according to prior warfarin usage. Apixaban, or matching placebo, was administered with the standard dose being 5 mg twice daily. A lower dose of 2.5 mg twice daily was used in a subset of patients if they had two or more of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or a serum creatinine greater than 1.5 mg/dL. Warfarin was administered and the dose adjusted to achieve a target INR of 2.0 to 3.0. INRs were monitored with the use of a blinded and encrypted point-of-care INR device. An algorithm was provided to guide the adjustment of warfarin or matching placebo dose.

The primary efficacy endpoints were stroke and systemic embolism. Death from any cause and myocardial infarction were key secondary efficacy endpoints. The primary safety endpoint was the occurrence of major bleeding defined as clinically overt bleeding accompanied by a decrease in hemoglobin level of at least 2 g/dL, a requirement for a two-unit packed cell transfusion, or bleeding in a critical site or resulting in death. Efficacy and safety outcomes were adjudicated on the basis of prespecified criteria by a blinded clinical events committee.

Over a 40-month period, 18,201 patients were recruited at 1034 international sites. The groups were well balanced with regard to baseline characteristics with a median age of 70 years, a 65%:35% male:female gender ratio, and a means CHADS2 score of 2.1. Notably, 30% of the patients in both groups had CHADS2 scores ≥ 3. Vitamin K antagonists had previously been used in 57% of the patients and 19% had a history of a prior stroke, TIA, or systemic embolism.

The reduced dose of apixaban (2.5 mg twice daily) or placebo was administered to 428 patients in the apixaban group and 403 patients in the placebo group. Study drug discontinuation was observed in 25.3% of the patients on apixaban vs 27.5% in patients on placebo. Patients on warfarin had an INR in the therapeutic range, a median of 66% of the time.

Stroke or systemic embolism occurred in 212 patients in the apixaban group for an annual rate of 1.27%. In comparison, stroke or systemic embolism occurred in 265 patients in the warfarin group yielding a rate of 1.6% per year. The hazard ratio for the apixaban group was 0.79 with a 95% confidence interval of 0.66 to 0.95. The P value for noninferiority was less than 0.001 and equal to 0.01 for superiority. Hemorrhagic stroke was 49% lower in the apixaban group than in the warfarin group and ischemic or unclassifiable stroke was 8% lower in the apixaban group. The rate of fatal or disabling stroke was 0.5% per year in the apixaban group compared to 0.71% per year in the warfarin group. Among the patients who had ischemic strokes, hemorrhagic transformation was noted in 12 patients on apixaban and 20 patients on warfarin. Fatal strokes were noted in 42 patients in the apixaban group and 67 patients in the warfarin group. All-cause mortality was lower in the apixaban group (3.52% per year) than in the warfarin group (3.94% per year). There was no significant difference in the rate of myocardial infarction between the two groups (0.53% and 0.61%).

Major bleeding occurred at an annual rate of 2.13% in the apixaban group compared to 3.09% in the warfarin group. The rate of intracranial hemorrhage was reduced to 0.33% per year in the apixaban group compared to 0.80% per year in the warfarin group (hazard ratio 0.42; 95% confidence interval, 0.30 to 0.58; $P < 0.0001$). The rate for any bleeding was 25.8% per year in the warfarin group compared to only 18.1% in the apixaban group. Fatal bleeding occurred in 34 patients in the apixaban group compared to 55 patients in the warfarin group.

Subgroup analysis showed consistent beneficial effects of apixaban across all major subgroups. Overall, reported adverse events were equally distributed between the two groups. There were no differences in the frequency of abnormalities in liver function tests or liver related serious adverse events between the two groups.

The authors conclude that in patients with

nonvalvular atrial fibrillation, apixaban is superior to warfarin for the prevention of stroke or systemic embolism with less risk for bleeding and a lower overall mortality.

■ COMMENTARY

This is the third large clinical trial showing that a new oral anticoagulant is noninferior or superior to warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. Dabigatran, a direct thrombin inhibitor, was assessed in the RE-LY trial and the result of that trial led to dabigatran's FDA approval last year. Earlier this summer, the ROCKET AF trial compared rivaroxaban, a factor Xa inhibitor, to warfarin in a similar group of patients. The ARISTOTLE trial reported here again shows that a factor Xa inhibitor compares favorable to warfarin for this indication. I suspect that both rivaroxaban and apixaban will join dabigatran as being approved for this indication within the next year. Several similar agents are also in the clinical development pipeline.

These trials have been enormous, each enrolling more than 18,000 patients. It's unlikely there will be more than one or two such trials for each agent. There are no head-to-head comparisons available or, to my knowledge, planned directly comparing the new agents. Conclusions or claims based on comparisons across different trials are likely to be uncertain. I think we can say that the new agents at the tested doses are at least as effective and safe as adjusted-dose warfarin and certainly they will be easier to prescribe. If the increased cost of the new agents were not a factor, I would likely pick one and use it for initial therapy in most patients with nonvalvular atrial fibrillation. Right now, I don't see evidence that any of the new agents will be clearly superior, but we should watch closely for any later arising problems that may be seen during general usage. ■

ABSTRACT & COMMENTARY

Subclinical Stroke in AF Ablation

By John P. DiMarco, MD, PhD

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SOURCE: Siklody CH, et al. Incidence of asymptomatic intracranial embolic events after pulmonary vein isolation. Comparison of different atrial fibrillation ablation technologies in a multicenter study. *J Am Coll Cardiol* 2011;58:681-688.

In this study, Siklody and her colleagues from three large and experienced atrial fibrillation (AF) ablation centers performed cerebral magnetic resonance imaging before and after AF ablation using three different catheter technologies. Patients were eligible for inclusion if they had symptomatic drug-resistant AF and were referred for a catheter ablation. Patients with longstanding persistent AF, patients in whom left atrial ablation other than pulmonary vein isolation, and those with contraindications to cerebral magnetic resonance imaging (MRI) were excluded. Three different ablation catheter technologies were evaluated in the study. These included conventional irrigated radiofrequency (RF) ablation catheters (either CoolPath Duo or Thero-Cool), an Arctic Front cryoballoon ablation catheter, or a multielectrode duty-cycled phased RF pulmonary vein ablation catheter (Medtronic Ablation Frontiers). Ablations were performed by operators at the individual institutions with expertise in these respective techniques. Standard RF ablation procedures were performed at all three centers, cryoballoon ablations in one center and phased RF pulmonary vein catheter ablations in two centers.

All three of these catheters are available for routine clinical use in Europe. Recommended techniques were used in each. For conventional pulmonary vein isolation with externally irrigated catheters, a double transseptal technique was used. The cryoballoon pulmonary vein isolation procedure used a single transseptal puncture. For phased RF pulmonary vein isolation using a multielectrode catheter, a single transseptal approach was also used.

Patients were treated before the procedure with 4 weeks of oral anticoagulation. Anticoagulation was reduced or stopped two to three days before ablation and bridging with low molecular weight heparin was permitted if necessary. Patients underwent a transesophageal echocardiogram on the day before ablation to rule out left atrial thrombi. During the procedure, intravenous unfractionated heparin was administered immediately after the first transseptal access. Anticoagulation was resumed after the

procedure with heparin bridging if necessary until the INR was greater than 2.5.

A systematic neurologic exam was performed on admission, the day after the procedure, and 4-5 days after the procedure. Cerebral MRI was performed 1 day before and 1-2 days after ablation using a 1.5-T unit. Two experienced radiologists blinded to the ablation technique analyzed all MRI scans. A third radiologist was used in cases of disagreement.

The study included 74 patients. There were slightly more patients with persistent AF in the externally irrigated RF group. Left atrial size and thromboembolic risk profiles were similar between the groups. Seventeen of the 74 patients presented in AF, and AF was noted during the procedure in another 10 patients. Twenty-three patients underwent electrical DC cardioversions during the procedure. These characteristics were evenly distributed in all three groups. All pulmonary veins were successfully isolated with all three techniques. Procedural and fluoroscopy times were longest in the externally irrigated RF group, intermediate in the cryoballoon group, and shortest in the pulmonary vein ablation catheter group.

No patient had new neurologic symptoms after the procedure and standard neurological examination in all patients were normal before and after ablation. Chronic lesions on the baseline MRI before ablation were noted in six patients in the externally irrigated RF group, two in the cryoablation group, and one in the pulmonary vein catheter ablation group. After the procedure, MRI revealed new ischemic lesions in 2 of 27 (7.4%) patients in the externally irrigated RF group, in 1 of 23 (4.3%) in the cryoballoon group, and in 9 of 24 (37.5%) in the pulmonary vein ablation catheter group. In the latter group, these patients presented with a median of three acute lesions on postprocedure MRI. The increased incidence of new ischemic lesions in the pulmonary vein ablation catheter group was statistically significant. The new lesions could be distributed over both hemispheres, but were preferentially located in the vertebrobasilar territory. The median lesion size was 5.5 mm. There was no difference in the details of procedural anticoagulation that could be related to the finding of new emboli.

The authors conclude that pulmonary vein isolation applied with the multielectrode duty-cycled phased RF ablation catheter used in this study is associated with an increased incidence of intracranial emboli that are fortunately subclinical. Further studies to clarify the causes and clinical significance of these embolic lesions should be performed.

■ COMMENTARY

Until recently, no ablation catheter was approved specifically for pulmonary vein isolation during AF ablation procedures. Now several externally irrigated RF ablation catheters and a cryoballoon system have been approved for use in the United States and the multielectrode phased RF system is available in Europe. The trials that led to these device approvals were relatively small and focused primarily on early and intermediate term efficacy and secondly on procedural safety. Routine cerebral MRI imaging was not included in the design of these trials.

Most surveys on the results of pulmonary vein isolation in AF patients show a per-procedural stroke rate of 0.5%-2%. This number is based on clinically manifest events. However, several small single-center reports, and now this three-center report, have shown that routine cerebral MRI imaging after the procedure can detect clinically silent new lesions. The current report suggests that the rate of these events may differ based on the catheter technology used. Although we don't now know the long-term significance of these lesions in individual patients, we must assume that they may have subtle adverse effects during follow-up.

The data presented here strongly argue that routine MRI imaging should be an additional feature included in protocols designed to evaluate new catheter technologies. Catheter associated with higher rates of new lesion formation should probably not be approvable. ■

ABSTRACT & COMMENTARY

ACE Inhibitors/ARBs for Aortic Stenosis?

By Andrew J. Boyle, MBBS, PhD

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

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 therapy. 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. ■

ABSTRACT & COMMENTARY

Progression of Diastolic Dysfunction Predicts Incident Heart Failure

By Andrew J. Boyle, MBBS, PhD
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SOURCE: Kane GC, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA* 2011;306:856-863.

Approximately half of all cases of heart failure occur in the context of normal systolic function (heart failure with preserved ejection fraction [HFPEF]) and the number of cases is projected to rise as the population ages. Diastolic dysfunction on echocardiography has been associated with HFPEF in cross-sectional studies. However, the effect of progression of diastolic dysfunction, assessed by serial echocardiograms, on the risk for subsequent heart failure is not known. Accordingly, Kane and colleagues studied the longitudinal changes in diastolic function over a 4-year period in a community cohort and then studied their incidence of heart failure in the subsequent 6 years.

In 1997, 4203 persons older than 45 years of age in Olmsted County, Minnesota, were invited to participate in the study. A total of 2042 participated in the first examination and 1402 returned for the subsequent examination 4 years later. Echocardiographic parameters of diastolic function included mitral inflow pulsed Doppler E/A ratio, pulmonary venous flow, and medial mitral annular tissue Doppler velocity. Participants were graded into four categories: normal diastolic function, mild, moderate, or severe diastolic dysfunction.

The mean age of the cohort was 65 years at the second visit, with 53% being younger than 65 years of age. More than 95% were white, 49% were male, and mean BMI was 28. Over the 4 years between the first and second echocardiogram, the prevalence of hypertension, diabetes, coronary artery disease, and heart failure all increased ($P \leq 0.001$). Accordingly, more patients were also taking cardiac medications at the second examination, and the recorded blood pressure was actually lower at the second examination. Diastolic dysfunction prevalence increased from 24% to 39% ($P < 0.001$). The prevalence of systolic dysfunction did not change and the mean ejection fraction actually increased (63.9% vs 65.9%, $P < 0.001$). Individuals demonstrated worsening diastolic function in 23%, unchanged diastolic function in 68%, and improved diastolic function in 9%, and worsening of diastolic function was significantly associated with age > 65 years (odds ratio 2.85).

During 6.3 years of follow-up after the second echocardiogram, the development of heart failure correlated with diastolic function at echocardiogram 2. The incidence of heart failure was 2.6%, 7.8%, and 12.2% in persons with normal diastolic function, mild diastolic dysfunction, and moderate or severe diastolic dysfunction, respectively ($P < 0.001$). Multivariable analysis identified the following five independent predictors of incident heart failure: age (hazard ratio [HR] 8.38), hypertension (HR 2.21), coronary artery disease (HR 2.07), diastolic dysfunction (HR 1.81), and diabetes (HR 1.77). The authors conclude that in a population-based cohort undergoing 4 years of follow-up, the prevalence of diastolic dysfunction increased and that diastolic dysfunction was associated with development of heart failure during 6 years of subsequent follow-up.

■ COMMENTARY

This longitudinal study demonstrates that over a short period of time (4 years), diastolic dysfunction occurred in nearly one-quarter of the cohort. This is a staggeringly high number in view of the fact that the majority of the cohort was younger than 65 years of age. In addition, the power of diastolic dysfunction to predict subsequent heart failure was of a similar order of magnitude to diabetes, hypertension, and coronary artery disease. This has prognostic implications not only for our elderly patients, but also for our middle-age patients. Unfortunately, the therapeutic implications remain unclear. Is there some way to impact the development of heart failure in patients diagnosed with diastolic dysfunction? Currently that remains unknown, and we can only control risk factors such as hypertension as best we can, and recommend adherence to diet and lifestyle modifications that are shown to be of long-term benefit.

This study is strengthened by the longitudinal nature of the serial echocardiographic evaluations. Furthermore, because Olmsted County residents are studied longitudinally, the authors were able to

compare the outcomes of those who did not return for the second examination with those who did return. Nonreturners often confound observational studies, but not this study. Here, nonreturners had more co-morbidities and a higher subsequent mortality. Thus, the fact that they did not return for follow-up likely underestimated the effects of diastolic dysfunction on subsequent heart failure. There are several limitations to the study. First, the population was almost completely white, and so the results may not be generalizable to other populations. In fact, it would be reasonable to expect that the prevalence of diastolic dysfunction may be even higher in other ethnic or racial groups. Second, we are not told of how progression of diastolic dysfunction affects the risk of heart failure. The participants were classified according to their diastolic function at the second visit, not according to the change in diastolic function over the 4-year period. Thus, we are left to ponder the role of change in diastolic function in the management of these patients. Finally, we are not told what factors were associated with deteriorating or improving diastolic function. Do diet or lifestyle factors, obesity, or even medications change one's diastolic function over time? More study in this area is needed, but for now, we should consider diastolic dysfunction a marker of risk for heart failure and recommend adherence to diet and lifestyle factors that may improve outcomes. ■

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CME Questions

1. The overall risk of MI or cardiac arrest in the general perioperative patient is:
a. < 1%.
b. 1-2%.
c. 3%.
d. 4%.

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

3. The factor Xa inhibitor apixaban compared to warfarin for atrial fibrillation patients results in:
a. less bleeding complications.
b. lower mortality.
c. fewer strokes
d. All of the above

4. MRI detected subclinical cerebral lesions are detected more commonly following which atrial fibrillation ablation technique?
a. Irrigated radiofrequency catheter
b. Cryoballoon catheter
c. Multielectrode phased RF catheter
d. None of the above

5. Which of the following is most correct concerning LV diastolic dysfunction?
a. Its frequency increases with age.
b. It is associated with heart failure.
c. Worsening is related to hypertension.
d. a and b

CME Objectives

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

- discuss the most current information related to cardiac illness and the treatment of cardiac disease;
- explain the advantages and disadvantages, as well as possible complications of interventions to treat cardiac illness;
- discuss the advantages, disadvantages, and cost-effectiveness of new and traditional diagnostic tests in the treatment of cardiac illness; and
- discuss current data regarding outpatient care of cardiac patients.

PHARMACOLOGY WATCH

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

Apixaban is Heating Up the Anticoagulation Market

In this issue: Apixaban could soon join the anticoagulation market; Chinese herbs for flu; chronic medication and discontinuation after hospitalization; and FDA actions.

Apixaban trial results look promising

There is soon to be a third player in the anticoagulation wars. Apixaban, an oral factor Xa inhibitor, will likely soon join dabigatran and rivaroxaban as alternatives to warfarin for preventing stroke in patients with atrial fibrillation (AF). Dabigatran, a direct thrombin inhibitor, was approved for this indication last year and rivaroxaban, also a factor Xa inhibitor, is likely to be approved in early September. (Rivaroxaban was previously approved for DVT prevention in patients undergoing orthopedic surgery.) Apixaban also looks very promising based on results of the ARISTOTLE trial, which was published online in the *New England Journal of Medicine* on August 28. ARISTOTLE enrolled 18,201 patients with AF and at least one additional risk factor for stroke. Patients were randomly assigned to apixaban 5 mg twice daily or warfarin with a target INR of 2-3. ARISTOTLE was designed as a noninferiority study with a primary outcome of ischemic or hemorrhagic stroke, or systemic embolism. After median follow-up of 1.8 years, the rate of the primary outcome was 1.27% per year in the apixaban group vs 1.60% in the warfarin group (hazard ratio [HR] 0.79; 95% confidence interval [CI] 0.66 to 0.95; $P < 0.0014$ noninferiority; $P = 0.01$ for superiority). The rate of major bleeding was 30% less with apixaban and the rate of death from any cause was 3.52% with apixaban and 3.94% with warfarin ($P = 0.047$). The rate of hemorrhagic stroke in the apixaban group was about half that in the warfarin group (0.24% per year vs 0.47% per year, $P < 0.001$) and the rate of all other strokes was 0.97% with apixaban vs 1.05% with warfarin ($P = 0.42$). The authors conclude that in patients with AF, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality (*N Engl J Med* published online August 28, 2011). An excellent accompanying editorial discusses the seminal studies that compared the three new anticoagulants to warfarin for stroke prevention in patients with AF: RE-LY — dabigatran; ROCKET AF — rivaroxaban; and ARISTOTLE — apixaban. All three showed that the new drugs were significantly better than warfarin at reducing hemorrhagic stroke and all were at least as effective as warfarin at preventing ischemic stroke. All three drugs were also associated with a significantly lower rate of serious bleeding compared to warfarin. Apixaban was the only drug that showed a significant reduction in overall mortality, although both dabigatran and rivaroxaban showed trends in that direction. ROCKET AF has been criticized because the warfarin comparator group had a time in therapeutic range of only 55% compared to 64% in the RE-LY trial and 62% in ARISTOTLE; however, patients in the ROCKET AF study were at higher risk for stroke than in the other two studies. The bottom line is that all three drugs are effective in preventing stroke in patients with nonvalvular

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AF and seem to be safer than warfarin as well. The new drugs do not require any laboratory monitoring, which is convenient for patients and also lowers the overall cost of care (although all three drugs will be priced significantly higher than generic warfarin). Rivaroxaban has the advantage of a once daily dose vs the other two drugs, which must be dosed twice daily. None of the three drugs can be quickly reversed in the event of major bleeding or need for surgery. Apixaban is not yet approved in this country but when it is, it is likely that the competition between these three agents will be fierce, and for many purchasers of health care it may come down to cost. ■

Chinese herbs for flu treatment

For the flu season this year, you might consider Chinese herbs instead of antivirals based on the results of a study from China published in the *Annals of Internal Medicine*. More than 400 adults age 15-59 years with confirmed H1N1 influenza were randomized to oseltamivir 75 mg twice daily or a combination of 12 Chinese herbal medicines called maxingshigan-yinqiaosan 200 mL four times a day, a combination of oseltamivir plus maxingshigan-yinqiaosan, or placebo for 5 days. The primary outcome was time-to-fever resolution and the secondary outcomes included symptom scores and viral shedding. Both oseltamivir and maxingshigan-yinqiaosan, as well as the combination, resulted in significant reductions in the estimated median time-to-fever resolution compared to the control group (median time-to-fever resolution — no treatment 26 hours; oseltamivir 20 hours; maxingshigan-yinqiaosan 16 hours; combination 15 hours; all statistically significant at $P < 0.001$). Side effects were similar in all groups. The authors conclude that oseltamivir and maxingshigan-yinqiaosan, alone or in combination with each other, reduce time-to-fever resolution in patients with H1N1 influenza. They go so far as to suggest that maxingshigan-yinqiaosan may be used as an alternative treatment for H1N1 infections (*Ann Int Med* published online August 26, 2011). It may be difficult to obtain maxingshigan-yinqiaosan since it contains ephedra (which is not available in this country) and the authors could not determine if the benefits of maxingshigan-yinqiaosan were due to an antiviral effect or merely an antipyretic effect. ■

Chronic medications and hospitalization

Your patients' chronic medications may be inadvertently discontinued after hospitalization according to a population-based cohort study of almost 400,000 patients published recently in the *Journal of the American Medical Association*. Researchers from Canada reviewed the records of residents age 66 or older who were on statins, antiplatelet/anticoagulant agents, levothyroxine, respiratory inhalers, or gastric acid suppressing drugs on a chronic basis. When compared to nonhospitalized patients, patients admitted to the hospital — especially the ICU — were more likely to have their chronic medications discontinued. Discontinuation rates ranged from a low for levothyroxine of 12.3% discontinuation for hospitalizations vs 11% for controls, to antiplatelet/anticoagulant agents which were discontinued at a rate of 19.4% for hospitalizations vs 11.8% for controls. The discontinuation rates were even higher for patients who were admitted to the ICU. The authors conclude that patients admitted to the hospital are at relatively high risk for potential unintentional discontinuation of chronic medications (*JAMA* 2011;306:840-847). This study points out the importance of medication reconciliation at all post-hospital visits and may validate the role of computerized medical records, especially with regard to medication lists. ■

FDA actions

The FDA has approved a new fixed-dose combination pill for HIV-infected patients. Emticitabibine/rilpirivine/tenfovir DF is approved as a once-a-day pill for treatment of HIV-1 infection in treatment-naïve patients. This is the second triple combination anti-HIV agent approved and differs from the previous agent (Atripla) in that it contains the NNRTI rilpirivine rather than efavirenz. The new combination will be marketed as Complera.

The FDA has approved brentuximab vedotin to treat Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma. The drug is approved for HL patients who have progressed after autologous stem cell transplant or after prior chemotherapy regimens and cannot receive a transplant. This represents the first the drug to treat HL since 1977. Brentuximab will be marketed as Adcetris.

The FDA has approved vemurafenib for the treatment of metastatic and unresectable melanoma, specifically in patients whose tumors have the BRAF V600E mutation. The approval was accompanied by a companion diagnostic test that will determine if a patient's melanoma cells have that mutation (about half of the patients with late stage melanomas). Only patients with the BRAF V600E mutation will respond to the drug since it targets the mutated protein that regulates cell growth. Vemurafenib is marketed by Genentech as Zelboraf. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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

VOLUME 16, NUMBER 10 PAGES 19-20 OCTOBER 2011

Encouraging News About Lung Cancer Screening Benefits

Source: National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011; 365:395-409.

Screening for lung cancer by means of chest X-ray (CXR) does not reduce mortality, even with the addition of sputum cytology. Because low-dose helical CT (LDCT) detects much smaller, earlier lesions, the National Cancer Institute initiated a clinical trial in 2002 to determine whether LDCT screening, as compared to CXR, could reduce lung cancer (LCa) mortality.

Criteria for inclusion included at least a 30-year pack history of cigarette smoking, but if patients had signs of potential current LCa (e.g., hemoptysis, unexplained weight loss), they were not included. Study subjects were randomized to LDCT (n = 26,722) or CXR (n = 26,732) and underwent imaging at baseline, 1 year later, and 2 years later. Over the course of three screenings, 39% in the LDCT group and 16% in the CXR group had positive findings, of these more than 94% were false-positive — i.e., they were *not* LCa.

Evaluation of positive screening led to the diagnosis of LCa in 1060 of the LDCT group and 941 in the CXR group, so LDCT successfully identified about 13% more LCa. At 6 years of follow-up, LCa-related mortality was 20% lower in the LDCT group than the CXR group, and all-cause mortality was also 6.7% lower (both were statistically significant). Before widespread adoption of LDCT occurs, it has been suggested that cost-effectiveness analyses be performed, especially since the absolute risk reduction in mortality within the total study population was very small (1.31% vs 1.62%). ■

Treatment of Depression in Patients with Dementia

Source: Banerjee S, et al. Sertraline or mirtazapine for depression in dementia (HTA-SADD): A randomised, multicentre, double-blind, placebo-controlled trial. *Lancet* 2011;378:403-411.

The evidence base supporting efficacy of antidepressant pharmacotherapy in patients with dementia is sparse and inconsistent. Banerjee et al performed a double-blind, randomized, placebo-controlled trial in patients with dementia and depression to assess the effects of two commonly used antidepressants: sertraline and mirtazapine.

Study subjects were randomized to sertraline 150 mg/d (n = 107), mirtazapine 45 mg/d (n = 108), or placebo (n = 151) with no other changes in their medical regimen. Each active antidepressant was initiated at a low dose and titrated within 4 weeks to a higher dose if depression scores had not substantially improved. Outcomes were measured with the Cornell Scale for Depression in Dementia (CSDD).

At the conclusion of the trial, neither sertraline nor mirtazapine provided improvements in CSDD scores greater than placebo, but side effects were more frequent in the active treatment arms. Although the authors do not provide any specific suggestions about what treatments might be preferred (beyond counseling) in the face of these disappointing results, their outcomes suggest reconsideration of preferred treatment for patients with depression associated with dementia. ■

Comparing Metrics for Identification of Prediabetes

Source: Heianza Y, et al. HbA1c 5·7-6·4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): A longitudinal cohort study. *Lancet* 2011; 378:147-155.

Since more than half of newly diagnosed diabetics have one or more of the complications of diabetes already existing by the time of diagnosis, it is clear that we must strive for earlier identification of persons destined to develop diabetes and try to forestall or prevent it. The category "prediabetes" includes persons with impaired fasting glucose ([IFG] = 100-125 mg/dL), impaired glucose tolerance ([IGT] 2-hr PPG = 140-199), or elevated A1c (A1c = 5.7-6.4). In most prior clinical trials of diabetes prevention, inclusion required the presence of IGT, with or without IFG, since IGT was felt to be a better predictor of likelihood

to progress from prediabetes to diabetes. In clinical practice, very few prediabetes patients are identified by glucose tolerance testing because of the cumbersome nature of the testing. Because utilization of A1c has only recently been condoned as a diagnostic tool for prediabetes, it is worthwhile to peruse the results of an observational trial that followed adults (n = 6241) without diabetes at baseline and compared the predictive capacity of A1c and IFG.

Over 4.7 years of follow-up, more than twice as many individuals developed IFG (n = 1680) than increased A1c (n = -822), and of course some (n = 410) developed both. The predictive capacity of A1c alone was quite similar to IFG alone, but since the two groups have only modest overlap, A1c and IFG actually define somewhat different populations destined to become diabetic. Hence, the authors suggest that using both measurements at the same time is necessary to capture the largest segment of persons with prediabetes. ■

Accuracy of Stated Energy Contents of Restaurant Foods

Source: Urban LE, et al. Accuracy of stated energy contents of restaurant foods. *JAMA* 2011;306:287-293.

Eating out has increased in the general population, and is associated with increased body mass index. Indeed, United States data suggest that more than one-third of all daily calories are provided from restaurants. If clinicians and their patients want to make more healthful choices when eating out, they must rely to some degree on the listed caloric content of these foods, but have little assurance that such listings are accurate.

Urban et al performed bomb calorimetry on 269 food items from 42 different restaurants, and compared calorimetry results with caloric content listed by restaurants.

Nineteen percent of the sampled foods were substantially (more than 100/kcal) above their listed energy content when tested with calorimetry. At the highest decile of discrepancy, foods averaged greater than 250 kcal/portion more than their restaurant listings indicated. It is estimated that eating an extra 100 kcal/d on a chronic basis could result in 5-15 kg of weight gain per year. Encouragingly, the overall food caloric assessments stated in restaurants were reasonably accurate; in the minority of cases where inaccuracies underestimate caloric content, health-conscious consumers may be getting more than they bargained for. ■

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

Executive Editor: Leslie Coplin.
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The Past and Future Burdens of Violence Against Women

Source: Rees S, et al. Lifetime prevalence of gender-based violence in women and the relationship with mental disorders and psychosocial function. *JAMA* 2011;306: 513-521.

More than 20% of adult American women report being victims of rape, intimate partner violence, or stalking. Limitations of previous data sets preclude identifying associations between lifetime experiences of violence and subsequent mental health issues.

Rees et al performed an analysis of data from the second Australian National Mental Health and Well-being Survey, which included 4451 adult women ages 16-85. The overall lifetime prevalence of any mental disorder (as per DSM–IV criteria) was 37.8% including anxiety disorder (24.6%), mood disorder (18.3%), substance use disorder (13.9%), and post-traumatic stress disorder (9.8%). One or more of the above mentioned forms of violence was reported by 27.4% of these same women.

Data analysis found that victims of violence were more likely to also experience mental health disorders; additionally, the severity of these victims' mental health disorders was greater, as was the likelihood that more than one mental health disorder would ensue. The authors suggest that the magnitude of the burden of violence against women and its mental health sequelae merit an enhanced public health focus on the problem. ■

Does Androgen Deprivation Improve Outcomes for Localized Prostate Cancer?

Source: Jones CU, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med* 2011;365:107-118.

Antiandrogen treatment has been shown to induce tumor cell regression in some androgen-responsive cancers, including some prostate cancers. Unfortunately, the survival benefits seen in clinical trials with long-term antiandrogens have been tempered by increased adverse effects, including erectile dysfunction and myocardial infarction. Jones et al performed a controlled trial of radiotherapy for men with localized prostate cancer (n = 1979), with or without short-term (4 months) androgen-deprivation treatment (goserelin or leuprolide).

Overall 10-year survival in patients receiving androgen-deprivation treatment was statistically significantly greater than in men who only received radiotherapy (62% vs 57%). Prostate cancer-associated mortality was also superior in the group receiving androgen-deprivation treatment (8% vs 4%). Black men enjoyed the same degree of risk reduction as non-blacks.

Hepatotoxicity did occur in a minority of men treated with androgen-deprivation treatment, but was low-grade in more than 95% of cases. Short-term androgen deprivation improves outcomes in men with localized prostate cancer. ■