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CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

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ACE Inhibitors for Patients with Normal Left Ventricular Function

ABSTRACTS & COMMENTARY

By Michael H. Crawford, MD

Sources: Dagenais GR, et al. Angiotensin-Converting-Enzyme Inhibitors in Stable Vascular Disease without Left Ventricular Systolic Dysfunction or Heart Failure: A Combined Analysis of Three Trials. *Lancet*. 2006; 368:581-588; Remuzzi G, Ruggenenti P. Overview of Randomised Trials of ACE Inhibitors. *Lancet*. 2006;368:555-556.

Angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce mortality and myocardial infarction (MI) in patients with heart failure due to reduced left ventricular (LV) systolic function. Three recent trials have evaluated ACE inhibitors in patients with vascular disease, but normal LV systolic function: HOPE, EUROPA, and PEACE. Although targeted at similar patients, using a similar design, there were differences between the studies. Thus, Dagenais and colleagues explored the consistency of the outcomes between these studies and their variation due to other ancillary therapy or levels of risk. All 3 trials included > 8000 patients each, and followed them for about 5 years. The results were compared to the results of a similar analysis of 5 large ACE inhibitor trials in patients with LV dysfunction or heart failure. The combined results of HOPE, EUROPA, and PEACE showed that ACE inhibitors reduce many end points vs placebo: all-cause mortality from 8.9 to 7.8%; cardiovascular mortality from 5.2 to 4.3%; MI from 6.4 to 5.3%; stroke from 2.8 to 2.2%; and heart failure from 2.7 to 2.1%; all $P < .001$. Coronary artery bypass surgery was also reduced from 6.9 to 6.0%; $P < .01$, but not percutaneous interventions (7.6 to 7.4%; P = ns). The composite end point of mortality, MI or stroke was reduced from 12.8 to 10.7% (OR, 0.82; CI, 0.76-0.88, $P < .0001$). These results were similar, but not exactly the same as those of the 5 large heart failure trials of ACE inhibitors. Dagenais et al concluded that ACE inhibitors reduce major adverse cardiac events in patients with atherosclerotic vascular disease but no known LV dysfunction and, thus, ACE inhibitor therapy should be considered in all vascular disease patients.

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COMMENTARY

The thrust of this analysis is for us to ignore the differences in results between the 3 trials of ACE inhibition in chronic vascular disease patients without known LV dysfunction, and embrace this therapy for a broader range of patients. The 3 trials combined include almost 30,000 patients and, per this analysis, show an 18% reduction in major adverse coronary and cerebral events, with a number needed to treat to prevent one event of 48 patients. Current ACC/AHA guidelines for unstable angina/non-ST elevation MI patients and chronic stable angina patients recommend ACE inhibitors prophylactically only for LV ejection fraction (ejection fraction) < .40 and diabetes, and therapeutically for systolic heart failure and hypertension. Should we be using ACE inhibitors for all vascular disease patients regardless of LV function? The editorial that accompanied this article thought not, due to several deficiencies in this study.

The major problem with this study is that it was not a meta-analysis. Individual data were not available from the 3 trials, so summary data were used, which may obscure individual trends. Also, the patient populations in these studies were different. In HOPE, 80% had coronary artery disease (CAD), whereas it was 100% in the other 2 studies. Eight percent of HOPE patients had LV EF < .40, whereas it was < 1% in the other 2. Antiplatelet therapy was given to 76% in HOPE and > 90% in the other 2. Beta-blocker use was 40% in HOPE and > 60% in the other 2. The use of lipid-lowering therapy increased from 29% in HOPE to 57% in EUROPA, to 70% in PEACE. The individual study results got progressively less impressive as the risk level of the patients decreased and the drug therapy intensified. In HOPE, significant gains were seen in all major cardiac events, except heart failure. EUROPA was significant for all end points, except total mortality and stroke. PEACE, which had the lowest risk patients on the most medications, was only significant for less heart failure in the ACE inhibitor group. Thus, one could argue that in lower-risk CAD patients on aggressive medical therapy, the addition of ACE inhibitor is not valuable. At this time, I would stick to the ACC/AHA guidelines until more persuasive data come along, and only use ACE inhibitors prophylactically for CAD patients with LV systolic dysfunction or diabetics. ■

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Ace Inhibitors for Abdominal Aortic Aneurysms

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *ACE inhibitors are associated with a reduced risk of ruptured abdominal aortic aneurysm, unlike other antihypertensive agents. Randomised trials of ACE inhibitors for prevention of aortic rupture might be warranted.*

Source: Hackam DG, et al. Angiotensin-Converting Enzyme Inhibitors and Aortic Rupture: A Population-Based Case-Control Study. *Lancet*. 2006;368:659-665.

RUPTURE OF AN ABDOMINAL AORTIC ANEURYSM (AAA) is a lethal complication of this relatively common (5% of men > 50 years of age) condition. Currently, early surgery is the only known preventative measure. Animal studies suggest a role for angiotensin II in the pathogenesis of AAA, and ACE inhibitors have been shown an ability to prevent aortic expansion and rupture. Other antihypertensive drugs were not effective, suggesting that this effect may be independent of blood pressure reductions. Thus, Hackam and colleagues performed a retrospective, case-controlled study of ACE inhibitor use in AAA patients in Ontario Province, Canada.

A database was used to identify 15,326 patients age 65 or older who were hospitalized with a primary diagnosis of intact or ruptured AAA over 10 years (1992-2002). The primary exposure was ACE inhibitor treatment before hospitalization derived from pharmacy records and defined as 2 or more prescriptions in the year before admission with 1 within 3 months of admission. Logistic regression analysis was used to compute any association between ACE inhibitor use and AAA rupture, and multivariate analyses were used to assess the effects of confounders. Also, the exposure to 5 other antihypertensive drug classes was assessed in a similar fashion.

Results: Rupture occurred in 22% of the patients with a mean age of 75 years; 78% were men. Ace inhibitors before admission were found in 22% of the total population, and the indications for their use between the rupture and no rupture groups was the same. Patients receiving ACE Inhibitors had an 18% lower risk of rupture (OR, 0.82; CI, 0.74-0.90; $P < 0.0001$). Adjustment for confounders did not appreciably alter the results. The benefit was not related to ACE inhibitor dose or type of ACE inhibitor. Discontinuation of ACE inhibitor before admission abrogated the benefits. Ace inhibitors were effective in all pre-specified subgroups. Other antihypertensive agents were not associated with a reduced risk of rupture. Hackman et al concluded that ACE inhibitors are associated with a reduced risk of AAA rupture.

COMMENTARY

Here is another study attempting to broaden the indications for ACE inhibitors. This study is based upon solid pre-clinical data. It showed benefit if you were taking ACE inhibitors and none if you discontinued them. The benefit was not seen with other classes of drugs. The main issue in any case-controlled study is selection bias. This is a hospital-based study, so those who ruptured out of the hospital are not included. Perhaps those on ACE inhibitors were healthier in general and less likely to rupture. Against this is that there was no difference in the indications and contraindications for ACE inhibitors between those taking and not taking them. Also, adjustment for comorbidities and other confounders did not change the results. Thus, the data seem solid.

The fact that other antihypertensives were not associated with this benefit suggests that the beneficial effect is due to some other effect of blocking the renin-angiotensin system. Unfortunately, there is no blood pressure data in this study. Also, no dose response to ACE inhibitors was seen, suggesting that the effect is not related to blood pressure lowering. There was insufficient data in the study to ascertain if the effect is also seen with angiotensin receptor blockers.

The management of AAA is now predicated on following the diameter of the aorta and recommending surgery or endovascular repair for certain sizes. Although I would not prescribe ACE inhibition instead of surgery for those with large aneurysms, I certainly would try to get those who are not surgical candidates on ACE inhibitors, based upon this data. Since the effect was not dose related, the minimal tolerated dose would probably be adequate. ■

Bleeding with Acute Coronary Syndrome

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *In ACS patients without persistent ST-segment elevation, there is a strong, consistent, temporal, and dose-related association between bleeding and death.*

Source: Eikelboom JW, et al. Adverse Impact of Bleeding on Prognosis in Patients with Acute Coronary Syndromes. *Circulation*. 2006;114:774-782.

MULTIPLE ANTITHROMBOTIC DRUGS COMBINED WITH aggressive percutaneous revascularization strategies has resulted in reports of major bleeding rates of up to 5% in acute coronary syndrome (ACS) patients. These rates are similar to the incidence of major ischemic events in these conditions, yet clinicians favor this aggressive approach to reduce the incidence of ischemia. Thus, Eikelboom and colleagues evaluated 3 large ACS trials to determine the prognostic import of major bleeding. The OASIS Registry, OASIS-2, and CURE trials had over 30,000 patients with ACS, but without ST elevation myocardial infarction (MI). Major bleeding was defined as bleeding requiring 2 or more units of blood transfused, or life-threatening bleeding. The latter was defined as fatal bleeding; intracranial; hemoglobin decrease of 5 g/dL or more; hypotension requiring pressors; surgical intervention required; or 4 or more units of blood transfused. The primary outcome was 30-day mortality. Secondary end points included MI and stroke. Associations with type of antithrombotic agent, dose, and risk of bleeding were examined.

Result: The overall incidence of major bleeding over the 3 trials was 2.3%; 2% of which occurred in the first 6 months with the biggest increment in the first 30 days. Patients who developed major bleeding were older, diabetic, had prior stroke, had lower blood pressure, higher creatinine, and ST changes on ECG. Also, they were more likely to receive glycoprotein IIb/IIIa agents, heparin, warfarin, fibrinolytics, coronary angiography, bypass surgery, or intraaortic balloon pumping. In addition, they had a higher incidence of death in the first 30 days (12.8% vs 2.5% for no major bleeding, $P = .002$). Finally, there was a progressive increase in risk of death going from minor to major to life-threatening bleeding. Major bleeding also increased the risk of MI and stroke. Eikelboom et al concluded that in ACS patients without ST elevation MI, there is a strong association between major bleeding and death.

COMMENTARY

The strength of this analysis is that it includes over 30,000 patients from 3 studies, with the same definition of major bleeding used. It is unlikely that a randomized trial of bleeding will ever be done because you cannot predetermine who will bleed. However, the results are robust and consistent, even after adjusting for comorbidities. Also, the risk of death increases with the severity of bleeding. Major bleeding increases mortality 5-fold and ischemic events 4-fold in the first 30 days. Herein lies the rub. Once major bleeding occurs, all antithrombotic agents are stopped, leaving the patient vulnerable to recurrent ischemic events. Thus, it is desirable to prevent major bleeding so that antithrombotic therapy can be continued. How can this be done, since major bleeding was shown to be associated with the use of these agents?

Several approaches come to mind. This study clearly showed that there is a risk profile for major bleeding. However, they are the older, sicker patients who need aggressive therapy the most. One factor associated with major bleeding was serum creatinine, and we know that certain antithrombotic agents such as low molecular weight heparin need to be adjusted for renal insufficiency. We don't have details about appropriate dosing in these trials, but I wouldn't be surprised if it was not perfect. Also, until we have more data about combinations of antithrombotic medications, it is wise to stick to current guidelines. For example, there is little data about the safety of clopidogrel and the glycoprotein IIb/IIIa inhibitors in combination. We currently do not give both together unless a coronary stent has been placed. Finally, newer agents may prove to be superior. Recent data on the direct thrombin inhibitor bivalirudin are encouraging in this regard.

The trials all excluded patients at the highest risk of major bleeding so, in actual clinical practice, the incidence of major bleeding is probably higher. In the trials, the overall risk of death due to major bleeding is < 1%, so we get lulled into a sense of security with these patients. The real world experience is not so rosy. This is clearly an area where diligence will pay off. Be sure not to overdose antithrombotics for the individual patient and use only those proven to be of benefit in a given situation. ■

Atrial Fibrillation

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

Dr. DiMarco is a consultant for Novartis, and does research for Medtronic and Guidant.

Source: Fuster V, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation — Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee For Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). *J Am Coll Cardiol*. 2006;48: 854-906.

THE 2006 GUIDELINES FOR THE MANAGEMENT OF patients with atrial fibrillation clarify previous recommendations for anticoagulation to prevent other thromboembolic events. The new guidelines focus on the number of risk factors that are present and the risk of bleeding in the individual. Estimates of stroke risk are based on the CHADS2 scoring system. This system gives one point each for the presence of cardiac failure, hypertension, age over 75, and diabetes, and 2 points for a history of stroke or transient ischemic attack (TIA). There is a graded increase in stroke risk as the CHADS2 score rises. Based on these data, the 2006 Guidelines recommend that patients should first be evaluated for risk factors.

They use the following definitions: High risk factors include previous stroke, TIA or embolism, mitral stenosis, or a prosthetic heart valve; Moderate risk factors include: age greater than or equal to 75 years, hypertension, heart failure, left ventricular ejection fraction 35% or less, and diabetes mellitus; Finally, they suggest that physicians should also consider the following less well-

validated or weaker risk factors: female gender, age 65 to 74, coronary artery disease, and thyrotoxicosis. For patients who have no risk factors, the recommendation is aspirin in a dose range of 81 mg to 325 mg daily. For patients with one moderate risk factor, either aspirin 81 mg to 325 mg daily or warfarin (International Normalized Ratio [INR] 2.0-3.0, target 2.5) may be used, with a decision based on risk of bleeding and patient preference. Presumably, the additional presence of one of the weaker risk factors would influence this decision. Finally, any patient with a single high risk factor or more than one moderate risk factor should receive warfarin (INR 2.0-3.0; target 2.5). These anticoagulation recommendations hold whether or not the patient has paroxysmal or persistent atrial fibrillation, since the stroke risk appears to be similar in trials that have looked at both groups.

The revised guidelines also discuss anticoagulation around the time of elective pharmacologic or electrical cardioversion. Previous studies have shown a risk of stroke or systemic thromboembolism after cardioversion between 1% and 5%. The new guidelines continue to recommend anticoagulation with warfarin (INR, 2.0-3.0) for 3 to 4 weeks before, and for at least 4 weeks after, cardioversion. The new guidelines now recognize the validity of a transesophageal echocardiography-based approach. With the latter, the duration of pre-cardioversion anticoagulation may be shortened if a transesophageal echo shows no thrombus in the left atrial appendage. It is important with this approach, however, that anticoagulation be maintained from the time of the transesophageal echo until at least 4 weeks after the procedure. The duration of anticoagulation after cardioversion should be based on the likelihood that atrial fibrillation will recur in the individual patient and on the risk of thromboembolism in the presence of atrial fibrillation as estimated by a system such as the CHADS2 scoring system.

As in previous guidelines, anticoagulation is not thought to be necessary in patients with atrial fibrillation of less than 48 hours duration. Although Fuster and colleagues recognize that there are only limited data on patients with atrial flutter only, they suggest that the same anticoagulation guidelines for patients with atrial flutter should be followed.

COMMENTARY

The new guidelines clarify some previous recommendations about anticoagulation for patients with atrial fibrillation. The new guidelines place a greater dependence on a risk scoring system, such as the CHADS2 scoring system. The major change in the guidelines relates to patients whose CHADS2 score places them at intermediate risk of thromboembolism (3%-5% per year). In these patients, anticoagulation warfarin is no longer mandated and aspirin is listed as an acceptable alternative.

In any individual patient, the risk of stroke must be balanced against the risk of bleeding. Since the consequences of stroke are so high, I prefer to advise warfarin for patients at intermediate risk. I think one moderate risk factor plus a weaker risk factor should make one favor warfarin. Risk for bleeding should also be considered in these intermediate-risk patients. If patients are unwilling or unable to tolerate warfarin, then aspirin remains the alternate choice. ■

Embolic Risk Post Ablation

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Synopsis: *Discontinuation of anticoagulation 3-6 months after successful atrial fibrillation ablation is reasonable in low-risk patients.*

Source: Oral H, et al. Risk of Thromboembolic Events after Percutaneous Left Atrial Radiofrequency Ablation of Atrial Fibrillation. *Circulation*. 2006;114:759-765.

In this study, Oral and colleagues from the University of Michigan reviewed their experience with stroke and systemic thromboembolic events associated with percutaneous catheter ablation procedures for atrial fibrillation (AF). Oral et al reviewed data from 755 consecutive patients with paroxysmal or persistent (here called chronic) atrial fibrillation who underwent left atrial catheter ablation between January 2003 and July 2005. The population was mostly middle aged (55 ± 11 years) and included 577 men and 178 women. The AF pattern was paroxysmal in 490 patients and persistent in 265 patients. During their initial evaluation, the following risk factors for stroke were identified: congestive heart failure, hypertension, age greater than 65, diabetes mellitus, and prior stroke or transient ischemic attack (TIA).

All patients received low molecular weight heparin injections for 5 days prior to the procedure. Patients with persistent atrial fibrillation or with a history of either a stroke or a documented left atrial thrombus

underwent a transesophageal echocardiogram in the 24 hours before the ablation attempt. During left atrial mapping and ablation, heparin was administered to maintain an activated clotting time between 300 and 350 seconds. Once the ablation catheters and sheaths had been removed and hemostasis achieved, intravenous heparin was restarted and maintained overnight. Low molecular weight heparin at a dose of 0.5 mg/kg twice per day was then continued during warfarin treatment until the INR was ≥ to 2.0. All patients continued warfarin for at least 3 months after the procedure, with a desired INR of 2.0 to 3.0. In patients without risk factors, warfarin was discontinued at this point, and these patients were advised to take aspirin chronically. Patients with risk factors were advised to continue warfarin.

In the entire group, 411 patients (56%) had one or more risk factors for stroke, with hypertension being the most commonly identified risk factor. The remaining 344 patients (44%) had no risk factors. In the entire group, 32 (4%) had a history of congestive heart failure, 325 (43%) had a history of hypertension, 126 (17%) were over age 65, 55 (7%) had diabetes, and 34 (5%) had a prior stroke or TIA. Thromboembolic events were observed in 7 of 755 patients (0.9%) within 30 days of their ablation procedure. One event occurred with 6 hours of the procedure, 3 occurred one to 7 days after the procedure, and the remaining 3 occurred one to 2 weeks after the procedure. Six of the 7 patients with an early thromboembolic event had one or more risk factors for stroke. All patients with early events were between ages 51 and 67. In 5 of these 7 patients, deficits completely resolved. There were only 2 thromboembolic events beyond 30 days after the procedure. Both occurred in men, aged 40 and 55, with persistent AF. One of these patients had hypertension and diabetes, whereas the other had no risk factors. Both of the latter patients had therapeutic INRs at the time of their event. AF was present at the time of 5 of 7 early events and one of 2 late events.

At a median of 4 months after the ablation procedure, anticoagulation was discontinued in 203 of 256 (79%) patients who remained in sinus rhythm and did not have risk factors for stroke. Among the 266 patients who remained in sinus rhythm and had more than one risk factor, anticoagulation was discontinued in 180 (68%), at a median of 5 months after the procedure. Two hundred thirty-three patients had recurrent AF or atrial flutter after ablation, and 218 of these (94%) were continued on warfarin. There were 2 major bleeding complications in this series. Both occurred in patients being treated with warfarin who also had recurrent AF.

Oral et al conclude that their data suggest that discontinuation of warfarin 3 to 6 months after left atrial catheter ablation in patients without baseline risk factors for stroke is reasonable.

COMMENTARY

Stroke is the most feared adverse consequence of atrial fibrillation. Since left atrial catheter ablation was first introduced as a potential treatment for atrial fibrillation, the procedure has been shown to be effective in preventing or reducing the burden of recurrent arrhythmia in selected populations. However, the frequency of stroke, as a complication of the procedure itself, and the long-term effects of left atrial catheter ablation on stroke incidence have not been well characterized. In this paper, Oral et al showed that the acute stroke rate with left atrial catheter ablation is reasonably low. They also show that the intermediate-term stroke rate is low if the procedure is effective in eliminating arrhythmia at least in low or intermediate risk patients.

It has been estimated that there are over 2 million people in the United States who have some form of atrial fibrillation. The majority of these patients are elderly, and many have several other risk factors for stroke. As admitted by Oral et al, much more experience will be needed before we will know if left atrial catheter procedures are effective and safe in these higher risk populations. ■

Another New Biomarker for Cardiovascular Disease

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque

Dr. Abrams serves on the speaker's bureau for Merck, Pfizer, and Parke-Davis.

Synopsis: *Among elderly persons without chronic kidney disease, cystatin C is a prognostic biomarker of risk for death, cardiovascular disease, and chronic kidney disease.*

Source: Shlipak MG, et al. Cystatin C and Prognosis for Cardiovascular and Kidney Outcomes in Elderly Persons without Chronic Kidney Disease. *Ann Intern Med*. 2006;145:237-246.

MANY REPORTS OF BIOMARKERS FOR EVALUATION OF cardiovascular disease (CVD) risk have appeared

over the past several years. High sensitivity CRP and brain natriuretic peptides (BNP) are the most familiar, contributing to the evaluation of patients with and without CVD. BNP and its inactive precursor, Nt-proBNP, are markers for ventricular muscle stretch and congestive heart failure. Cystatin C, a new biomarker candidate, is the focus of a report from the Cardiovascular Health Study (CHS), a community based longitudinal study of adults > 65 years old at baseline. This cohort is the background for an extensive analysis of cystatin C as marker of prognosis for CV death, chronic kidney disease (CKD), and CVD. Cystatin C represents an alternative measurement of glomerular filtration rate (GFR), and may be a superior marker for prognosis of CKD than the standard MDRD (Modification of Diet in Renal Disease) estimate of GFR, (discussed in the same issue: Levy, et al. *Ann Intern Med*. 2006;145:237-246). The data from the CHS suggest that cystatin C provides a superior estimate of GFR, when compared to the MDRD formula, as it is independent of body muscle mass and unaffected by age or gender. Cystatin C is a member of a family of competitive inhibitors of lysosomal cysteine proteinases, and is involved in a variety of intracellular functions, including modulation of the immune system. Cystatin C levels (normal < 1.0 mg/L) have been found to be elevated in elderly patients with a GFR > 60, suggesting that this compound may better detect individuals at risk for subsequent CKD, death, or CVD than MDRD.

The CHS consists of 4 sites around the United States who enrolled relatively healthy patients > 65 years of age. The analysis consists of 4663 CHS participants followed for a median of 9.3 years, with serial measurements of creatinine and cystatin C. GFR was measured using the MDRD formula; CKD was diagnosed by an estimated GFR < 60 mL/min per 1.73 m^2. The primary end point included new CKD, as well as various cardiovascular events (death, stroke, heart failure, and myocardial infarction). All subjects were evaluated for GFR (MDRD formula), mean cystatin C, and creatinine concentration. Patients were categorized into 3 baseline groups: CKD; no CKD but high cystatin C (> 1.0 mg/L); and no CKD and low cystatin C.

Results: Seventy-eight percent of the study cohort (4663 participants) had no CKD at entry; 22% of CKD subjects had low GFR, a high cystatin C concentration, and elevated creatinine. Patients without CKD had normal values for all 3 parameters. Serum creatinine was not associated with subsequent mortality, but elevated cystatin C was associated with increased mortality, with increased risk beginning at > 1.0 mg/L. Two-fold risk occurred when levels were at 1.3-1.4 mg/L. Thus, CVD risk was related to baseline cystatin C but not baseline creatinine. In individuals without CKD, elevated cystatin C was associated with increased adverse events, including CV death, heart failure, and stroke. Event rates for all-cause CVD death, non-cardiovascular death, heart failure, and stroke were lowest in individuals who had no CKD and low cystatin C levels at baseline. Baseline CKD predicted increased risk for adverse events. Individuals without CKD who had high elevated cystatin C "were 50% more likely to die, were nearly twice as likely to have a cardiovascular death, and were 30% more likely to have a non-cardiovascular death." Heart failure, stroke, and myocardial infarction rates were also substantially increased. Patients who had no CKD and high cystatin at baseline developed CKD far more often than those with low baseline cystatin (odds ratio 4- to 5-fold). Participants with high cystatin C who developed CKD during the study were at substantially higher risk for death and cardiovascular events, with increased risk ranging from 35% for stroke to 80% for CVD death and heart failure.

Finally, enrollees with elevated cystatin C at baseline and no CKD during the study also had a greater risk for death, heart failure, and myocardial infarction. Levy and colleagues summarize, "whereas serum creatinine levels had almost no statistically significant associations with the outcomes . . . cystatin C concentrations were strongly related with risk for death, heart failure, myocardial infarction, and stroke." Forty percent of the entire cohort had elevated cystatin C levels without CKD at baseline; the subjects had substantially increased risk for death, cardiovascular risk, and progression to CKD. Levy et al believe the data support that "a state of pre-clinical kidney disease . . . is prevalent among elderly persons." They make the analogy to pre-hypertension or pre-diabetes as being as potentially eligible for prophylactic treatment. Thus, elevated baseline cystatin C with preserved GFR was associated with increased risk for a variety of events. "Cystatin C concentrations seem primarily to reflect GFR, and do so better than serum creatinine." Cystatin C was felt to be a better predictor of subsequent kidney function than MDRD GFR. Overall, elevated cystatin C was clearly a marker for major adverse events.

Levy et al conclude, "We believe that elevated cystatin C concentrations represent preclinical kidney disease, which portends increased cardiovascular and renal risk." They call for further studies, particularly

to define the role of micro-albuminuria vs cystatin C as a major risk factor for CVD and renal outcomes, asking "whether cystatin C . . . will have a useful clinical role."

COMMENTARY

While this report focuses on individuals who were > 65 of age at entry into the study, and clearly defines cystatin C as a marker of subsequent adverse events, including death, one does not know if cystatin C would have a comparable predictive value in younger healthy individuals. In any case, it would appear that cystatin C is an excellent predictor of GFR, as opposed to serum creatinine. It is generally accepted, particularly in the elderly populations, that creatinine levels between one and 2 are very difficult to interpret, with respect to the degree of GFR abnormality. It may not yet be fully appreciated that CKD is now identified as an important marker for cardiovascular risk, and should be included in any risk stratification algorithm. The current study suggests that in a healthy, older population, an elevated cystatin C imparts considerable risk for the development of CKD and/or for major cardiovascular events. It would be of great interest to see whether these findings are reproducible, and to see if the use of cystatin C assays may amplify the risk profile for CVD and mortality, particularly in younger individuals. Whether routine measurements of cystatin C will become available remains to be seen, but this study, as well as other data in the literature, clearly indicates that renal function, as estimated by creatinine concentration, albuminuria, or cystatin C, is a major risk factor for vascular events, and is much more common than many of us would have believed. ■

CME Questions

17. Rupture of an abdominal aortic aneurysm may be prevented by:
a. ACE inhibitors.
b. replacement surgery.
c. endovascular repair.
d. All of the above

18. Prophylactic ACE inhibitors are indicated for:
a. diabetes patients.
b. low left ventricular function.
c. CAD patients without diabetes or reduced LV function.
d. a and b

19. Anticoagulation for chronic atrial fibrillation is preferred for:
a. high-risk patients.
b. intermediate-risk patients.
c. low-risk patients.
d. All of the above

20. Minimal duration of anticoagulation following catheter ablation of atrial fibrillation is:
a. one month.
b. 2 months.
c. 6 months.
d. one year.

21. Major bleeding following hospitalization for acute coronary syndrome increases:
a. mortality.
b. myocardial infarction.
c. stroke.
d. All of the above

22. Prognostic markers for cardiovascular morbidity and mortality in older individuals include:
a. chronic kidney disease.
b. creatinine.
c. cystatin C.
d. a and c

Answers: 17. (d); 18. (d); 19. (a); 20. (b); 21. (d); 22. (d)

CME Objectives

The objectives of *Clinical Cardiology Alert* are:

• To present the latest information regarding diagnosis and treatment of cardiac disease;

• To discuss the pros and cons of these interventions, as well as possible complications;

• To discuss the pros, cons, and cost-effectiveness of new and traditional diagnostic tests, and;

• to present the current data regarding outpatient care of cardiac patients. ■

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The Indictment of Pharma Industry Marketing Practices

A team from UCSF recently reviewed company documents that were entered into the public record as a result of litigation over the promotion of gabapentin (Neurontin) between 1994 and 1998. The result, a rather scathing indictment of the pharmaceutical industry's marketing practices, is published in the August 15 *Annals of Internal Medicine*.

The authors had access to thousands of pages of inside company documents from Pfizer, Parke-Davis, and Warner-Lambert regarding the marketing of gabapentin during a time that the drug was a blockbuster, with sales in the hundreds of millions of dollars.

The primary focus of the litigation was the promotion of off-label indications of gabapentin by Parke-Davis. The paper highlights the company's marketing strategy, which included identifying groups of physicians for targeted marketing. Local champion physicians were identified and trained as "peer-to-peer selling" program leaders. The company also identified physician thought leaders in academic medicine who were given large honoraria, research grants, and educational grants to promote the drug. Resident physicians were also targeted, and large sums of money were given to residency programs. Medical education was one of the cornerstones of the marketing plan.

Physician lectures, teleconferences, and other meetings were set up discuss treatment of epilepsy, but also to discuss off-label use of the drug. Parke-Davis employees frequently surreptitiously listened in on these meetings electronically, in part to gauge the effectiveness of the presentation. Physician moderators were paid well for their participation.

Parke-Davis also developed speaker's bureaus and created academic neurologic lecture series for the neurology community. Department chairs and clinical training program directors were frequently on the speakers lists of these programs. The company also gave unrestricted grants through third-party medical education companies which allowed speakers to legally discuss off label use of gabapentin and to grant CME credits.

A Parke-Davis memo describes these activities as a "growth opportunity" for off-label use of the drug. Physician advisory boards were also well paid to attend meetings where promotional activities were discussed. Research was also directed by the company, and there are indications that studies that gave favorable outcomes were more likely to be published than studies that were not favorable to the drug.

The company also promoted review articles and letters to the editor of journals regarding gabapentin for as much as the $18,000 per article. The authors point out that activities "traditionally considered independent of promotional intent" such as CME and research were corner-

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stones of marketing efforts, and when run through a third party, were legal marketing forums for off-label uses of the drug. The authors call for new strategies to "ensure a clear separation between scientific and commercial activity" (*Ann Int Med*. 2006;145:284-293). This paper is a must read for anyone involved in formulary management, cost effective prescribing processes, or medical education.

TNF Blockers: Should You Be Concerned?

The use of TNF blockers for treatment of rheumatoid arthritis has always been clouded by the potential risk of lymphoma or solid cancers. A new study suggests that the concern may be unfounded.

Researchers from Harvard and University of British Columbia performed a cohort study pooling data from 1152 RA patients who received a biologic DMARD (the TNF blockers etanercept, infliximab, adalimumab, or anakinra) and 7306 patients who received methotrexate. Both groups of patients had elevated risks of cancer compared to the general population, but the overall hazard ratio for hematologic and solid tumors for patients receiving a biologic DMARDs vs methotrexate was 0.98 (1.11 lymphoproliferative cancers 1.37 for hematologic malignancies, and 0.91 for solid tumors).

The authors conclude that biologic agents are unlikely to have a substantial increase in the risk of hematologic malignancies and solid tumors as compared with methotrexate users (*Arthritis Rheum*. 2006;54:2757-2764).

FDA Actions

The FDA has approved over-the-counter access for Plan B, the so-called morning-after pill. Over-the-counter sales of Plan B have been a contentious issue on Capitol Hill throughout the Bush presidency, and it took a change in leadership in the FDA to bring about the change in position. Plan B will be available for women ages 18 and older without a prescription; however, a prescription is still required for women ages 17 and younger. Plan B is marketed by Duramed, a subsidiary of Barr Pharmaceuticals.

Several SSRI antidepressants have made the switch to generic, including fluoxetine, paroxetine, citalopram, and sertraline. Now the first generic serotonin/norepinephrine reuptake inhibitor has been approved. Venlafaxine (marketed as Effexor) was approved for generic switch in August in 25 mg, 37.5 mg, 50 mg, 75 mg, and 100 mg strengths. TEVA pharmaceuticals have exclusivity on the generic for 180 days.

The FDA has approved the use of clopidogrel (Plavix -Bristol-Myers Squibb) in patients with ST segment elevation myocardial infarction (STEMI) who are not going to have coronary artery interventions. The new indication for the drug was based on the findings of 2 studies (COMMIT and CLARITY), which showed improved outcomes with use of the drug in STEMI patients, including those who had initial thrombolytic therapy.

In related news, a somewhat bizarre patent battle over clopidogrel is raging between Bristol-Myers Squibb and Canadian generic maker Apotex. The Canadian company challenged the patent, and introduced generic clopidogrel to the American market on August 8. On August 31, a federal judge in New York issued a restraining order to block distribution of the generic version of the drug; however, she did not require a recall of the generic pills already on the market. Bristol-Myers, which derives 30% of its yearly profit from sales of Plavix, is unsure how much generic product was distributed in 4 weeks; most estimates are approximately 3 months supply. Meanwhile, the patent trial is scheduled to begin in January.

The FDA's Center for Drug Evaluation and Research has issued a warning regarding concomitant use of ibuprofen and aspirin for patients who are taking aspirin for cardioprotection. Functional studies have shown that ibuprofen blocks the effect of aspirin on platelets if the 2 drugs are taken at the same time. Both drugs inhibit cyclooxygenase on platelets. Aspirin's effect is irreversible for the life of the platelet, whereas ibuprofen and other NSAIDs cause reversible inhibition. If ibuprofen is taken before or concomitantly with aspirin, the receptor site is occupied and aspirin is unable to exert its effect. However, if aspirin is taken 30 minutes before ibuprofen or 8 hours after, there is no competitive inhibition. The FDA is recommending that physicians be aware of the timing of ibuprofen and, perhaps, other NSAIDs when used with aspirin, and specifically recommend that aspirin be given 30 minutes prior to ibuprofen or 8 hours later. Recommendations regarding enteric-coated aspirin are unavailable at this time. ■