Providing Evidence-based Clinical Information for 24 Years

# CLINICAL CARDIOLOGY ALERT

*A monthly update of developments in cardiovascular disease*

Thomson American Health Consultants Home Page—www.ahcpub.com

CME for Physicians—www.cmeweb.com

THOMSON
AMERICAN HEALTH CONSULTANTS

## INSIDE



**Financial Disclosure:**

*Clinical Cardiology Alert's* physician editor, Michael H. Crawford, MD, is on the speaker's bureau for Pfizer. Peer Reviewer, Rakesh Mishra, MD, reports no consultant, stockholder, speaker's-bureau, or other financial relationship with any company related to this field of study.

# CABG vs PCI for Left Main Coronary Stenosis

ABSTRACT & COMMENTARY

***By Michael H. Crawford, MD***

**Source:** Lee MS, et al. Comparison of Coronary Artery Bypass Surgery with Percutaneous Coronary Intervention with Drug-Eluting Stents for Unprotected Left Main Coronary Artery Disease. *J Am Coll Cardiol*. 2006;47:864-870.

OBSERVATIONS WITH NEW DRUG-ELUTING STENTS HAVE SUGGESTED that percutaneous coronary intervention (PCI) on left main coronary artery stenosis unprotected by a bypass graft may be safe and effective. Therefore, Lee and colleagues at Cedars-Sinai Medical Center in Los Angeles report on the results of coronary artery bypass surgery (CABG) in 123 patients and PCI with drug-eluting stents in 50 patients treated after drug-eluting stents became available in 2003. The primary end point was freedom from major adverse cardiac and cerebrovascular events (MACCE) at 30 days and the end of follow-up (mean, 6 months). Comparison of the baseline characteristics of the 2 groups showed that the PCI group had fewer men, more chronic renal insufficiency, more patients with unstable angina, and more patients with a high surgical risk score (> 15 Parsonnet score). MACCE at 30 days for CABG was 17% and for PCI 2%, $P < .01$. The 6-month freedom from MACCE was 83% CABG and 89% PCI, $P = .2$. The results at 1 year were similar, and no component of the MACCEs was significantly different at 6 and 12 months of follow-up. In the 42% who had follow-up angiograms, freedom from target vessel revascularization at 6 months was 99% in the CABG group and 93% in the PCI group ($P = .22$). Multivariate analysis showed that the Parsonnet score, diabetes, and CABG were independent predictors of MACCE. Lee et al concluded that PCI for left main coronary artery stenosis is not associated with an increase in complications vs CABG for 6 months.

## COMMENTARY

This is an interesting trial because it shows what can be accomplished using a multidisciplinary clinical judgment approach to a high-risk clinical situation. Left main coronary artery stenosis is a

VOLUME 25 • NUMBER 4 • APRIL 2006 • PAGES 25-32

NOW AVAILABLE ONLINE
www.ahcpub.com

high-risk situation with a 20% 1-year mortality and a 50% 3-year mortality on medical therapy. The landmark VA study published in 1976 showed that CABG markedly reduced this mortality rate, and it has been the standard of care since. However, progress with PCI has suggested that it may be a competitive technique now and, perhaps, superior in selected patients. Thus, this experience with PCI for left main stenosis is timely.

Each patient was evaluated by an interventional cardiologist and a cardiac surgeon, and the best therapy was employed. Using this approach, less than one-third of the patients studied were allocated to PCI. Not surprisingly, those receiving PCI had significantly higher Parsonnet scores, as they were not ideal surgical candidates. So at the least the pre-procedure risk of both groups was comparable, yet there was a trend toward better outcomes with PCI, which diminished with time. A larger patient population may have shown statistical significance with some of the difference between PCI and CABG. On the other hand, a longer follow-up may have shown superiority of CABG. So, at this point PCI appears to be a viable alternative to CABG, especially when multidisciplinary clinical judgment is used to select treatment.

There are several limitations to this study. It is observational, so other biases may exist in patient selection beyond the baseline characteristics reported. There is no long-term follow-up. The sample size is small. Almost all the PCIs were done by one operator. The majority got Cypher stents. Biomarkers were not checked with either procedure. Finally, there was low compliance with follow-up angiograms. So, should a randomized, controlled trial be done? Perhaps, but it would only compare patients eligible for both procedures and eliminate clinical judgment. This may be a situation where careful observation of the results of clinical judgment may be sufficient to make sound recommendations. Clearly, more data are needed, but not necessarily a randomized trial.

It is worth pointing out that 64% of the PCI patients received intra-aortic balloon pumping prophylactically post procedure, but this may not turn out to be necessary. Also, only 14% of the PCI patients were treated with platelet glycoprotein IIb/IIIa agents because there is little experience with such agents in left main angioplasty; these patients are eliminated from most PCI trials. However, target vessel revascularization was low and exclusively seen in those with distal bifurcation lesions. CABG is probably best for these patients. Finally, Lee et al believe that in stent restenosis, post left main PCI should be treated with CABG. ■

*Clinical Cardiology Alert*, ISSN 0741-4218, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

**VICE PRESIDENT/GROUP PUBLISHER:** Brenda Mooney.
**EDITORIAL GROUP HEAD:** Lee Landenberger.
**MANAGING EDITOR:** Robert Kimball.
**ASSOCIATE MANAGING EDITOR:** Leslie Hamlin.
**MARKETING PRODUCT MANAGER:** Gerard Gernazian.

**GST Registration Number:** R128870672.

Periodicals postage paid at Atlanta, GA.

**POSTMASTER:** Send address changes to *Clinical Cardiology Alert*, P.O. Box 740059, Atlanta, GA 30374.


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



**Subscriber Information**

**Customer Service: 1-800-688-2421**
**Customer Service E-Mail:** customerservice@ahcpub.com
**Editorial E-Mail:** leslie.hamlin@thomson.com

**Subscription Prices**

**United States**
1 year with Free AMA Category 1 credits: $289
(Student/Resident rate: $125).

**Multiple Copies**
Documents are available for multiple subscriptions. For pricing information, please call Steve Vance at (404) 262-5511.

**Canada**
Add GST and $30 shipping.

**Elsewhere**
Add $30 shipping.

**Accreditation**

Thomson American Health Consultants is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

"Thomson American Health Consultants (AHC) designates this educational activity for a maximum of *25 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity."

AMA PRA Category 1 Credit is a trademark of the American Medical Association. Accredited providers are required to use AMA PRA Category 1 Credits™ whenever the complete phrase is first used in any publication, and periodically through the publication.

This CME activity is intended for the cardiologist. It is in effect for 36 months from the date of the publication.

**Questions & Comments**

Please call Leslie Hamlin, Associate Managing Editor, at (404) 262-5416 or e-mail at leslie.hamlin@ thomson.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

THOMSON
AMERICAN HEALTH CONSULTANTS

# 2-Year Experience with EECP

ABSTRACT & COMMENTARY

***By Michael H. Crawford, MD***

***Synopsis:*** *Decreased angina and improvement in quality of life were maintained at 2 years, with modest repeat EECP and low major cardiovascular event rates.*

**Source:** Soran O, et al. Two-Year Clinical Outcomes After Enhanced External Counterpulsation (EECP) Therapy in Patients with Refractory Angina Pectoris and Left Ventricular Dysfunction (Report From the International EECP Patient Registry). *Am J Cardiol*. 2006;97:17-20.

ENHANCED EXTERNAL COUNTERPULSATION (EECP) HAS been shown to be effective in reducing symptoms in patients with refractory angina and congestive heart failure, but little information exists about its long-term effectiveness in patients with marked left ventricular (LV) dysfunction and refractory angina. Thus, Soran and colleagues queried the International EECP Patient Registry (IEPR) for such patients. The IEPR includes > 5000 patients from > 100 centers world-

wide who received EECP for angina and were followed for up to 2 years. There were 363 patients with angina and LV ejection fraction ≤ 35%. After completion of treatment, 77% decreased at least one Canadian Cardiovascular Society Class, 18% had no angina, and 2% worsened. About half of the patients discontinued nitroglycerin use, and quality of life improved. After 2 years, the improvement in angina continued in over half of the patients. Event-free survival was 70%, and survival overall was 83%. Also, freedom from heart failure was 81%. Repeat EECP was performed in 20%, many of whom failed to complete the first treatment course. Improvements in quality of life were also maintained in most. Soran et al concluded that in patients with LV dysfunction and refractory angina, EECP improved quality of life and reduced angina for 2 years.

## COMMENTARY

Since EECP increases venous return during diastole, there has been concern that it may precipitate heart failure in patients with refractory angina and marked LV dysfunction. Pilot studies have shown benefit in heart failure patients and few heart failure events in angina patients with LV dysfunction. In this 2-year study, 81% of the patients were heart failure free. Thus, EECP seems safe in patients with marked LV dysfunction. Also, the beneficial effects seen immediately after EECP seem to persist for 2 years.

This is remarkable when you consider that most got one 32-hour course of therapy. Also, these were very sick patients. Angina class was III or IV in 93%, and 93% were deemed non-revascularizable. During EECP, 12% had a clinical event and 7% quit, but 81% completed the treatment. Noncompleters were a high-risk group that had more heart failure events. The 5% who did not respond to EECP were also a high-risk group who had more unstable angina admissions (28 vs 16%, $P = .02$) and a lower survival rate (71 vs 85%, $P = .001$).

The major limitation of this study is that it is observational and there is no control group. However, it is difficult to determine what would constitute an appropriate control group. Randomizing patients with refractory angina to EECP or placebo seems harsh at this point. Since most are non-revascularizable, revascularization does not seem to be the appropriate control. Perhaps in the future, the new anti anginal drug ranolazine would be a good comparison. It is just coming on the market for refractory angina patients. ■

# 64-Slice CT for Detecting CAD

ABSTRACT & COMMENTARY

***By Michael H. Crawford, MD***

***Synopsis:*** *In 94%, interpretable images were found. Accuracy was 95% for sensitivity, 96% for specificity, 97% for positive predictive value, and 92% for negative predictive value for lesions with > 50% stenosis.*

**Source:** Fine JJ, et al. Comparison of Accuracy of 64-Slice Cardiovascular Computed Tomography with Coronary Angiography in Patients with Suspected Coronary Artery Disease. *Am J Cardiol*. 2006;97:173-174.

The new 64-slice cardiovascular computed tomography (CVCT) is theoretically superior to the old 16-slice CT for detecting coronary artery disease (CAD). Thus, Fine and colleagues studied 66 consecutive patients who underwent CVCT and coronary angiography to diagnose obstructive CAD. Both procedures were performed within 30 days of each other. Patients with high heart rates were given beta-blockers to reduce their heart rate to 50-60 beats per minute for CVCT. The results of both studies were read independently by readers blinded to the other test results. A lesion of > 50% stenosis was considered significant. Also, left ventricular ejection fraction (EF) was determined by both techniques. Vessels < 1.5 mm in diameter were excluded from analysis, since CVCT is unreliable at this level of resolution. The angiography was considered the gold standard.

**Results:** Two hundred forty-five coronary arteries were evaluated in the 66 patients. CVCT was of diagnostic quality in 62 of the 66 (94%). In comparison to angiography, the sensitivity of CVCT was 95%, specificity 96%, positive predictive value 97%, and negative 92%. Vessel-by-vessel accuracy was 98% for the left main, 93% for the left anterior descending, 92% for the circumflex, and 92% for the right. Mean EF was identical for both techniques (59%). Fine et al concluded that CVCT is a reliable diagnostic test for suspected obstructive CAD.

## COMMENTARY

Clearly, the new 64-slice CVCT is superior to the older 16-slice technique for detecting significant CAD based upon previous studies; 16-slice CT was not done in this study. The issue is whether it is good enough to forgo angiography, unless catheter-based therapy is

indicated. This means how good is it at identifying normal vessels and mild disease, which hangs on the negative predictive value. Unfortunately, this has not changed with CVCT vs 16-slice CT; it is still about 92%. Is this good enough to send a chest pain patient home from the emergency department? I spoke to our seasoned, internal medicine oriented (as compared to surgical) ED doctors, and they said they were uncomfortable with this degree of accuracy until a clinically oriented trial is done. Such a trial would evaluate outcomes after CVCT to see what the myocardial infarction/death rate is with a normal or mild disease CVCT. On the other hand, a positive study for significant CAD may speed up getting the patient revascularized without the delays built into stress testing. Also, the positive predictive value is much higher at 97%, so referral to angiography is an acceptable approach.

There are a few caveats to CVCT. First, in about 5% it is of too poor a quality to interpret. Second, it requires a heart rate < 60 beats/min for the accuracy reported in this study. Patients who are hypotensive and tachycardic would not be good candidates. Third, the radiation exposure is considerable and higher than the average coronary angiogram. So is CVCT ready for prime time? Maybe not, but it is being installed or used all over the United States as you read this. It would be ideal if outcome study data were forthcoming soon. ■

# Value of Echocardiography for Detecting Mechanical Prosthetic Valve Dysfunction

ABSTRACT & COMMENTARY

***By Michael H. Crawford, MD***

***Synopsis:*** *In the aortic position, TTE and TEE allow a quantitative evaluation of leaflet(s) dynamics only in a minority of patients and cinefluoroscopy still remains the first-choice technique.*

**Source:** Muratori M, et al. Feasibility and Diagnostic Accuracy of Quantitative Assessment of Mechanical Prostheses Leaflet Motion By Transthoracic and Transesophageal Echocardiography in Suspected Prosthetic Valve Dysfunction. *Am J Cardio*l. 2006;97:94-100.

CINEFLUOROSCOPY (CF) HAS BEEN THE GOLD STANDARD for the evaluation of suspected mechanical prosthetic valve thrombosis, but only provides an analysis of leaflet motion. Echocardiography, either transthoracic (TTE) or transesophageal (TEE), could potentially evaluate leaflet motion and provide thrombus visualization, which may be more accurate for detecting valve thrombosis. Thus, Muratori and colleagues from Milan, Italy, studied 111 consecutive patients with suspected mechanical valve thrombosis (n = 71) or who were being evaluated prior to electrical cardioversion of atrial fibrillation (n = 40). The majority had bileaflet valves in either the aortic or mitral position. Each underwent TTE, TEE, and CF on the same day. Valve opening and closing angles on CF were compared to a reference group of normally functioning valves and values > 2 standard deviations were considered abnormal.

**Results:** CF found abnormal prosthetic valve function in 71 patients and normal function in 40. With the one exception of identifying normal mitral prosthesis function, TEE was superior to TTE. Since the specificity of TEE for mitral and aortic prostheses was 100%, so was the positive predictive value. Sensitivity was 100% with TEE of the mitral valve, so the negative predictive value was 100%. Sensitivity of detecting an abnormal aortic prosthesis by TEE was 85% and the negative predictive value was 94%. Valve leaflet opening and closing angles were correctly determined in all mitral prostheses using TEE, but in a minority of aortic prostheses. In all 40 patients who were treated for prosthetic valve dysfunction, the presence of thrombus was confirmed (38 at surgery, 2 with improvement after thrombolysis). Muratori et al concluded that mitral mechanical prosthetic valve dysfunction can be accurately detected by TEE, but in aortic prostheses CF is still the method of choice.

## ■ COMMENTARY

Since CF is considered the gold standard for diagnosing mechanical prosthetic valve dysfunction, one could argue that this simple test should be employed first to rule the diagnosis in or out. However, in many hospitals getting access to the catheterization laboratory and finding someone who is experienced at getting the correct imaging angle to make leaflet angle measurements is not always as easy as getting an echo done. Also, echo will provide other details that may explain the patient's symptoms, such as depressed LV function, new native valve disease, pericardial effusion, etc.; so in real life, a TTE is done first. The key findings on TTE are increased gradients across the prostheses, new regurgitation or, in some cases, obvious masses or fixed leaflets. Such findings by TTE in

the mitral position are diagnostic of prosthetic valve dysfunction, and further studies would only be confirmatory. A normal-appearing mitral mechanical prosthesis with a normal gradient and no new regurgitation is less helpful because up to one-third of proven malfunctioning mitral prosthetic valves will have these findings on TTE. TEE, however, is highly accurate for detecting mitral valve dysfunction, and could be the next step or CF can be done. In the aortic position, TTE is inaccurate, and TEE is only accurate if the valve is abnormal (positive predictive value 100%). So a normal-appearing TTE in the aortic position, as with the mitral position, requires further testing. In contrast to the mitral position with a normal-appearing TTE of the aortic prosthesis, TEE is not sufficiently sensitive; so, CF is the test of choice. To summarize, assuming most patients get TTE first, with an abnormal mitral prosthesis you are home free (100% accurate); any other result requires confirmation, which could be TEE or CF, with a CF preferred for a normal-appearing aortic prosthesis. ■

# Implantable Loop Recorder in Syncope Patients

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.*

***Synopsis:*** *In highly symptomatic patients with vasovagal syncope, the heart rhythm observed during spontaneous syncope does not correlate with the results of tilt table testing.*

**Source:** Deharo JC, et al. An Implantable Loop Recorder Study of Highly Symptomatic Vasovagal Patients: The heart Rhythm Observed During a Spontaneous Syncope is Identical to the Recurrent Syncope But Not Correlated with the Head-Up Tilt Test or Adenosine Triphosphate Test. *J Am Coll Cardiol*. 2006;47:587-593.

IN THIS REPORT, DEHARO AND COLLEAGUES CORRELATE THE tracings recorded by an implantable recorder during spontaneous episodes of syncope, with the results of provocative head-up tilt (HUT) and adenosine triphosphate (ATP) testing. Patients were included in the study if they met the following criteria: 1) a diagnosis of vasovagal syncope established by clinical criteria and provocative testing; 2) frequent episodes of spontaneous syncope; 3) an absence of structural heart disease; and 4) insertion of an implantable loop recorder (ILR—Medtronic Reveal or Reveal Plus). Baseline HUT was performed using a maximum of 45 minutes of tilt at a 60° angle. Nitroglycerine or isoproterenol challenge was used if the initial tilt was negative. The ATP test measured heart rate and blood pressure responses to a bolus intravenous injection of 20 mg of ATP.

The ILR was either patient activated only (3 patients) or set to automatically store heart rates below 40 beats per minute, above 165 beats per minute, or periods of asystole longer than 3 seconds.

Twenty-five patients met the study criteria. Their mean age was 60 years. They had a long history of syncope, with a mean of 7 episodes per year. All had a positive HUT, with a cardioinhibitory type response in 8 and a mixed response in 17. Seven patients had a positive response (> 6 seconds of asystole) during the ATP test. During follow-up after ILR insertion, 2 patients required early device removal. The other 23 completed the planned 18 months of follow-up. Eleven patients had no recurrent syncope. The remaining 12 patients experienced 31 episodes of recurrent syncope (2.6 ± 1.8 per patient). The ILR was activated by the patient during 23 episodes. In the other 8 episodes, automatic recordings were made during 2, but the remaining 6 did not trigger automatic activation excluding bradycardia in the latter. One patient experienced 6 episodes of recurrent syncope. One was associated with a 6-second pause after termination of an atrial arrhythmia, but recordings of the other 5 episodes, which were similar to her prior episodes, showed only sinus rhythm. The former episode was considered non-vasovagal and was not included in the rest of the analysis. A heart rate below 40 beats per minutes was recorded during 9 episodes in 5 patients. During these 9 episodes, sinus arrest (10.5 ± 6.2 seconds) was observed in 6, sinus bradycardia in 2, and sudden-onset atrioventricular block in one. Seven patients had more than one episode of vasovagal syncope. Each of these 7 had the same pattern of heart rate response during repeat episodes (heart rate > 40 beats per minute in 6 patients and < 40 beats per minute in 1 patient). Severe bradycardia during provocative testing did not predict bradycardia during clinical follow-up. Two of 4 patients with cardioinhibitory responses during HUT had bradycardia during spontaneous syncope. Two of 7 patients with vasodepressor/mixed responses during HUT had bradycardia. None of the 3 patients with asystole during ATP challenge manifested severe bradycardia during their clinical syncope, but 4 of 8 patients with a negative ATP test did.

Deharo et al conclude that in highly symptomatic patients with vasovagal syncope, heart rhythm responses during provocative HUT and ATP testing do not correlate well with observations made during spontaneous clinical episodes.

■ **COMMENTARY**

The value of provocative testing using either HUT or drug infusions in patients with recurrent, unexplained syncope remains controversial. When these tests were first introduced, they were enormously helpful in that they provided insights into the abnormal physiology associated with recurrent syncope. However, the value of these tests for making a diagnosis or for guiding therapy in an individual patient has proven to be disappointing. The diagnostic use of these tests is limited by a suboptimal sensitivity and specificity relationship. Day-to-day reproducibility of responses in individual patients is also poor, so that repeat testing is of little value. In this paper, we now see that hear rhythm responses during provocative tests in highly symptomatic patients with multiple episodes of syncope over many years do not predict the rhythm documented during later clinical episodes.

Patients with vasovagal syncope remain a challenge to clinicians. The diagnosis is best made on clinical grounds. If empiric therapy is not effective, the data in this paper suggest that ILR recordings rather than provocative test results should be used as guides to therapy. ■

# Wonder Drug Strikes Again!

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:*** *Use of statins in patients with atherosclerosis is associated with a reduced risk of subsequent sepsis. Randomized trials of statins for prevention of sepsis are warranted.*

**Source:** Hackam DG, et al. Statins and Sepsis in Patients with Cardiovascular Disease: A Population-Based Cohort Analysis. *Lancet*. 2006;367:413-418.

Several observational studies, as well as some animal research have suggested a beneficial role of statins in subjects with acute bacterial infection and sepsis. The hypothesis that statins may manifest non-lipid actions (pleiotropic effects) has been a popular theme for years. These drugs have effects on immune regulation, inflammation, and thrombogenesis, in addition to anti-oxidant actions and augmentation of nitric oxide. This Canadian study from the province of Ontario, postulated that statins may reduce the incidence of sepsis in a population of subjects with atherosclerosis.[1] This trial was a large scale, 5 year, population-based cohort study, and comprehensive analysis of sepsis events using propensity-matching to minimize confounding. A sophisticated statistical and epidemiological base underscores this study. Hackam and colleagues from Sunnybrook and Women's College Health Sciences Center in Toronto created a retrospective patient cohort of elderly individuals (> 65 years). They used 4 large validated data bases to identify appropriate individuals, and tracked consecutive patients admitted for a cardiovascular event or who had a revascularization procedure at any hospital in the province of Ontario between 1997 and 2001. All patients had acute coronary syndrome, acute ischemic stroke, or carotid or coronary revascularization procedure. Surveillance for statin use was carefully carried out by the Ontario Drug Benefit; all elderly patients in Ontario received universal prescription drug coverage through this formulary. Statin users were defined as individuals who had one of more prescriptions written during the 3 months preceding the index date, heralding the start of the analysis; nonusers had no statin prescription during this period. Propensity-based matching was utilized to establish a control subject for each individual who received a statin. The observation period began 3 months after hospitalization for each patient, and continued until death, hospital admission for sepsis, or termination of the study (March 31, 2002). The follow-up interval was subsequently extended to March 31, 2004. All sepsis admissions were identified. The primary analysis evaluated patients receiving a statin vs no statin. Eight pre-specified subgroups were identified who were felt to be at higher risk for development of sepsis. The association of statin use with the composite outcome of death, acute MI, and ischemic stroke was evaluated to, "check for the presence of an association where one would be expected."

**Results:** During the 5 year study, 173,000 individuals were hospitalized for vascular events. There were approximately 141,000 survivors at 90 days after discharge, one third of whom had received a statin during this period. Propensity-based matching was then carried out to create a final cohort of approximately 70,000 patients, half of whom received an initial statin prescription and half who did not. Statin users and controls were very similar with-respect to demographic characteristics, sepsis risk fac-

tors, and other healthcare markers. Diabetes, congestive heart failure, and COPD were common. Mean follow-up was 2.2 years, during which time 550 patients were admitted for sepsis in the statin group and 667 in the control group. Thus, the rate of sepsis was significantly lower for statin treated patients (71 vs 88 per 10,000 person/years, $P = 0.003$). The crude hazard ratio was 0.81, which was statistically significant. After adjustment for a variety of sepsis risk factor co-morbidities, there was still a 19% reduction in sepsis events. When adherence to therapy was evaluated, the association between statin use and sepsis was accentuated. Statin patients had fewer episodes of sepsis during the extended analysis and mean follow-up of 3.8 years. They also had a lower risk of severe and fatal sepsis than did controls. There was no obvious dose relationship with respect to the protective effects. Statin use was associated with a decrease in the composite of death, MI, and stroke (12% reduction). Non-statin lipid lowering drugs had no effect on sepsis incidence. Hackam et al conclude that the, "apparent protective association between statins and sepsis was consistent across several high-risk groups, was apparent throughout the entire follow-up period, and was amplified in analyses accounting for non-adherence and crossovers."

Hackam et al discuss statins and sepsis data and point out that their results are concordant with human and animal data on statins and sepsis; in 2 published studies of fewer than 400 patients each, statins had a marked salutary effect on sepsis mortality and progression of infection due to severe sepsis. In an animal model of sepsis, statin treatment led to "substantial reductions in inflammatory cytokines and activation of immune cells." This has also been found in humans. Statins have been shown to reduce excessive nitric oxide associated with shock and circulatory collapse, and appear to help maintain favorable hemodynamics in an animal model of polymicrobial sepsis. Furthermore, data has been positive for statin effects on several other bacterial, fungal, and viral pathogens. Hackam et al point out that their results are probably applicable to individuals without symptomatic atherosclerosis, such that cardiovascular co-morbidity is unlikely to be an important interaction. They conclude that statin use "was associated with a significantly reduced risk of sepsis, including severe sepsis and fatal sepsis." They suggest that individuals who are taking statins not stop their medications during serious infections, and that statins should not be discontinued routinely before high risk surgery. They even suggest that, "statins might be considered for patients at very high risk for sepsis," particularly if there is underlying cardiovascular disease. And finally, they call for future randomized control trials.

An accompanying editorial commentary is supportive of the study findings that there may be potential anti-inflammatory actions that are independent from the lipid effects of statins and that might be important in a variety of infections.[2] Hackam et al suggest that statin efficacy in sepsis is probably independent of lipid lowering actions, and is likely "to be mediated by interference with isoprenoid synthesis and subsequent geranylation of membrane proteins." Other studies have suggested anti-chlamydial action, as well as possible effectiveness against fungal and viral pathogens. They also call for large, placebo-controlled, randomized trials to assess statin prevention of sepsis, as well as treatment of overt sepsis. They emphasize the potential beneficial effect of these drugs in other arenas, including viral infections and even neurodegenerative disorders.[2]

## COMMENTARY

The hypothesis that statin drugs or HMG Co-A reductase inhibitors may have important biological effects in addition to, or separate from, LDL cholesterol lowering, has been around for years. There is an increasing number of manuscripts published suggesting statin efficacy in a variety of unrelated conditions, including congestive heart failure, atrial fibrillation, aortic stenosis, dementia, and the treatment of sepsis. If one examines the biochemical pathway beyond the HMG Co-A reductase step, it is clear that a variety of other processes may be affected when the parent enzyme is blocked. For instance, a rho-kinase inhibitor is being evaluated as a treatment of angina; this is an example of an interaction with moieties distal to the HMG Co-A reductase interaction. Prenylation of various proteins are affected by the use of statins, and this may have far reaching effects. A number of review articles have been published on this subject; 3 recent commentaries are recommended to the interested reader.[3-5]

In this careful, ambitious, and very large epidemiologic analysis of statin utilization in Ontario province, Hackam et al wanted to see if exposure to a statin would have a salutary effect of serious bacterial ( and perhaps other agents) infections and, in particular, sepsis. Using an unusual statistical design, they established a control group and a statin group of 35,000 patients each, and extracted information for an average of 2.2 years of subsequent evaluation for the development of sepsis and septic shock. Statin use did not have to be sustained, but was based on whether a statin was included in a patient's regimen several months after index hospi-

talization for an atherosclerotic event. The population studied had an acute coronary or cerebral event, or underwent revascularization, thus providing an appropriate rationale for statin utilization. Although only one third of the population was exposed to statins during the study period, the 2 equal groups, selected with the aid of a propensity analysis, appear to be large enough to produce a sufficient number of events for meaningful analysis. The degree of exposure and the dose and potency of statins are not available. Furthermore, the precise mechanism(s) of benefit cannot be ascertained from this study. The finding of an approximate 20% reduction in serious bacterial infections and sepsis in statin treated patients is remarkable. The type and nature of organisms are unknown. One must assume that sepsis was appropriately defined in the hospitals. Hackam et al,[1] as well as Merx and colleagues in an editorial commentary,[2] call for a randomized trial to further test the hypothesis that an HMG Co-A reductase inhibitor could have a beneficial effect on serious infections. The data certainly suggest this, although it does not seem appropriate to prescribe a statin as therapy in patients with sepsis until this hypothesis is accepted by the general medical community. Nevertheless, this is an exciting development, outpacing all of the other current hypotheses for pleiotropic statin effects in non-cardiac conditions. Hopefully, clinical trialists will quickly undertake an appropriately sized, placebo-controlled study that will resolve this question. ■

### References


1. Hackam DG, et al. Statins and Sepsis in Patients with Cardiovascular Disease: A Population-Based Cohort Analysis. *Lancet*. 2006;367:413-418.
2. Merx MW, Weber C. Statins: A Preventive Strike Against Sepsis in Patients with Cardiovascular Disease? *Lancet*. 2006;367:372-373.
3. Robinson JG, et al. Pleiotropic Effects of Statins: Benefit Beyond Cholesterol Reduction? A Meta-Regression Analysis. *J Am Coll Cardiol*. 2005;46: 1855-1862.
4. Ray KK, Cannon CP. Early Time to Benefit with Intensive Statin Treatment: Could It Be the Pleiotropic Effects? *Am J Cardiol*. 2005;96:54F-60F.
5. Ray KK, Cannon CP. The Potential Relevance of the Multiple Lipid-Independent (Pleiotropic) Effects of Statins in the Management of Acute Coronary Syndromes. *J Am Coll Cardiol*. 2005;46:1425-1433.


## CME Questions

**19. Sixty-four slice CT scanning vs coronary angiography shows:**
a. accuracies in the 92-98% range.
b. low radiation exposure.
c. feasibility in 100% of patients.
d. inaccurate EF estimates.

**20. Long-term results of EECP in LV dysfunction patients shows:**
a. a 90% event-free survival.
b. maintenance of the initial beneficial effects.
c. an Increased incidence of heart failure.
d. a 50% need for repeat EECP.

**21. TEE vs cinefluoroscopy for mechanical prosthetic valve dysfunction shows:**
a. an abnormal aortic valve echo is inaccurate.
b. a normal aortic valve echo is inaccurate.
c. an abnormal mitral valve echo is inaccurate.
d. a normal mitral valve echo is inaccurate.

**22. Statin drugs in vascular disease patients are associated with:**
a. a higher incidence of stroke.
b. a higher incidence of death, MI and stroke.
c. higher lipid levels.
d. a lower incidence of sepsis.

**23. In patients with frequent vasovagal syncope, heart rhythm is best predicted by:**
a. head up tilt-table testing.
b. pharmacologic challenges.
c. implantable loop recorders.
d. A & C

**24. Patients with left main coronary artery stenosis are best treated by:**
a. medical therapy.
b. surgery.
c. angioplasty.
d. B or C

**Answers:** 19. (a); 20. (b); 21. (b); 22. (d); 23. (c); 24. (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 current data regarding outpatient care of cardiac patients. ■

For access to your 2006 online bonus report, visit: www.ahcpub.com.

PHARMACOLOGY WATCH

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

# Can Calcium and Vitamin D Prevent Hip Fractures?

It has been a tough few months for marketers of vitamins and herbal products. Calcium plus vitamin D, saw palmetto, and glucosamine/chondroitin have all been the subject of studies that have questioned their efficacy. The calcium plus vitamin D results are possibly the most disappointing. In further data from the Women's Health Initiative study, 36,282 postmenopausal women ages 50 to 79 were randomly assigned to receive 1000 milligrams of elemental calcium with 400 IU of vitamin D3 or placebo, with the end point being prevention of hip and other fractures. After 7 years of follow-up, bone density was slightly higher, but there was no reduction in hip fractures in women who took calcium plus vitamin D (hazard ratio, 0.88 for hip fracture [95% CI, 0.72 to 1.08]). There was also no reduction in clinical spine fractures (HR, 0.90 [0.74 to 1.10]) or total fractures (HR, 0.96 [0.91 to 1.02]). Calcium plus vitamin D did result in a higher risk of kidney stones (HR, 1.17 [1.02 to 1.34]).

The authors conclude that among healthy postmenopausal women, calcium plus vitamin D supplementation did not significantly reduce hip fractures or reduce risks of kidney stones (*N Engl J Med*. 2006;354:669-683). In an accompanying editorial, Joel Finkelstein, MD, points out that many women who take calcium plus vitamin D "believe that they are completely protected against the development of osteoporosis. This study should help correct this important misconception and allow more women to receive optimal therapy for bone health." He also points out that women should not abandon calcium and vitamin D, neither should they rely on it alone as prevention against osteoporotic fractures (*N Engl J Med*. 2006;354:750-752 [correction published *N Engl J Med*. 2006;354:1102]).

### *Treatment of Benign Prostatic Hyperplasia*

Saw palmetto is used by over 2 million men to treat symptoms of benign prostatic hyperplasia (BPH). Now, a new study suggests that it is ineffective. The study, funded by the National Institutes of Health and the National Center for Complementary and Alternative Medicine, looked at 225 men over the age of 49 with moderate-to-severe symptoms of BPH who were randomized to one year of saw palmetto extract 160 mg twice a day or placebo. The primary outcomes were changes in American Urological Association Symptom Index and maximal urinary flow rates. Prostate size, the residual urinary volume after voiding, quality of life, laboratory values, and adverse effects were also measured. After one year, there were no significant differences between patients treated with saw palmetto or placebo in any of the outcomes. There was also no difference in adverse effects. The authors conclude that saw palmetto does not improve symptoms or objective measures of BPH (*N Engl J Med*. 2006;354:557-566). An accompanying editorial welcomes the scientific rigor of placebo-controlled trials applied to dietary supplements, which are generally not held to standards of safety and efficacy. The authors call for similar studies for other

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments? Please call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

commonly used herbal products (*N Engl J Med*. 2006;354:632-634).

### Treatment of Osteoarthritis of the Knee

Glucosamine and chondroitin sulfate is used by millions to treat osteoarthritis. In another study supported by the NCCAM, along with the National Institute of Arthritis and Musculoskeletal and Skin Diseases, 1583 patients with osteoarthritis of the knee were randomized to 1500 mg of glucosamine daily, 1200 mg of chondroitin sulfate daily, combination of glucosamine and chondroitin sulfate, 200 mg of celecoxib daily, or placebo for 24 weeks. Acetaminophen was allowed as rescue analgesia. The primary outcome was a 20% decrease in the pain from baseline at week 24. Glucosamine and conference sulfate were no better than placebo in reducing the pain by 20%, except for combined therapy (glucosamine plus chondroitin) in patients with moderate-to-severe pain at baseline (79.2% response vs 54.3% response placebo, $P = 0.002$). Adverse events were no different in all groups. The authors conclude that overall glucosamine chondroitin did not reduce pain effectively in patients with osteoarthritis of the knee, except in the subgroup of patients with moderate-to-severe knee pain (*N Engl J Med*. 2006;354:795-808). An accompanying editorial recommends telling patients that neither glucosamine nor chondroid alone has been shown to be more effective than placebo in treating knee pain. They suggest that glucosamine sulfate plus chondroitin sulfate may be tried in patients with moderate-to-severe knee pain, but should be discontinued after 3 months if there is no benefit (*N Engl J Med*. 2006;354:858-860).

### Refractory Asthma and TNF—Connection?

Refractory asthma is a condition with a high mortality rate and limited treatment options. A new study suggests that the tumor necrosis factor (TNF) axis is up-regulated in refractory asthma, creating the possibility of treating refractory asthma with TNF inhibitors. Researchers from the United Kingdom measured markers of TNF alpha activity in 10 patients with refractory asthma, 10 patients with mild/moderate asthma, and 10 controls subjects. Patients with refractory asthma increased expression of TNF alpha markers compared to those with mild-to-moderate asthma and controls. Study subjects with refractory asthma were subsequently randomized to receive the TNF alpha receptor etanercept 25 mg twice weekly in a placebo-controlled, double-blind, crossover pilot study. Ten weeks of treatment with etanercept was associated with a significant increase in concentration of methacholine required to provoke a 20% decrease in FEV1 ($P = 0.05$), an improvement in asthma related quality-of-life score ($P = 0$ .02), and a 0.32 liter increase in post bronchodilator FEV1 ($P = 0.01$) compared to placebo. The authors suggest that the TNF alpha axis is upregulated in refractory asthma, and that etanercept may be beneficial in these patients (*N Engl J Med*. 2006; 354:697-708). An accompanying editorial reports that several studies of TNF inhibitors in patients with refractory asthma are ongoing, suggesting that we soon should have an answer as to whether these agents are effective for treating this difficult clinical entity (*N Engl J Med*. 2006;354:754-758).

### FDA Actions

The FDA has approved anidulafungin, Pfizer's new anti-fungal for the treatment of candidemia. The drug is a new molecular entity that is given intravenously. It is approved for a variety of Candida infections including esophagitis, sepsis, abdominal abscesses, and peritonitis. It will be marketed by Pfizer as Eraxis.

The FDA has approved lubiprostone for the treatment of chronic idiopathic constipation in adults. The drug is a selective chloride channel activator that increases intestinal fluid secretion and motility. The drug will be marketed by Sucampo Pharmaceuticals as Amitiza.

CV Therapeutics has received approval to market ranolazine, the first of a new class of agents for the treatment of chronic angina. The drug is an orally available extended-release anti-anginal drug that acts without reducing heart rate or blood pressure. The drug's mechanism of action has not been fully characterized, but it is felt that it works by affecting changes in cardiac metabolism. Because ranolazine prolongs QT interval, it should be reserved for patients who have not achieved adequate response with other anti-anginal drugs, and should be used in combinations with amlodipine, beta-blockers, or nitrates. CV Therapeutics will market ranolazine as Ranexa.

The FDA has approved an oral vaccine for the prevention of rotavirus gastroenteritis in infants and children. The oral vaccine should be initiated in infants 6 to 12 weeks old, with 2 subsequent doses of 4 to 10 week intervals. The vaccine should be completed before the child reaches 32 weeks of age. Based on clinical trials, the vaccine appears to be 98% effective for preventing gastritis caused by targeted rotavirus serotypes, and 74% effective at preventing gastroenteritis of any severity. Rotavirus vaccine will be marketed by Merck as RotaTeq. ■