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INSIDE

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Prophylactic Revascularization Before Vascular Surgery

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Poldermans D, et at. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery. *J Am Coll Cardiol*. 2007;49:1763-1769. Moscucci M, Jones N. *J Am Coll Cardiol* 2007;42:1770-1771.

THE VALUE OF REVASCULARIZATION BEFORE MAJOR VASCULAR surgery in patients with stress induced myocardial ischemia has not been tested. Thus, the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) study was conducted in 5 European and 1 Brazilian hospitals. Among 1880 patients undergoing elective abdominal aorta or infrainguinal vascular surgery, 430 with 3 or more risk factors for coronary artery disease underwent dobutamine echo or dypridamole perfusion scintigraphy. The major inclusion criteria were extensive stress-induced ischemia which was present in 101 of the 430 patients. They were randomized to medical or revascularization therapy prior to surgery. All patients received perioperative beta-blockers at a dose to keep the resting heart rate between 50 and 65 beats/minute, as long as systolic blood pressure was > 100 mm Hg. Antiplatelet therapy was continued during vascular surgery. The primary endpoint was the composite of all-cause death and myocardial infarction (MI) until 30 days post surgery. The one-year death and MI rate was a secondary endpoint. Results: Two patients died between coronary artery bypass surgery (CABG) and vascular surgery of a ruptured aortic aneurysm. The primary endpoint was 43% in the revascularization group and 33% in the medical therapy group (OR 1.4, 95% CI 0.7-2.8, $P = 0.3$). Also, the primary endpoint was not different between those treated with CABG (performed in one-third) or percutaneous coronary revascularization (41% vs 44% during the 1-year follow-up). The authors concluded that perioperative coronary revascularization in vascular surgery patients with extensive stress-induced myocardial ischemia did not improved post operative or 1-year outcome.

COMMENTARY

The publication of the Goldman index in the 1970s lead to an industry of preoperative testing for patients with CAD or likely to

have it, based upon risk factors, to detect those with myocardial ischemia who were at highest risk of a perioperative coronary event. But detection implied treatment was necessary which spawned such absurdities as doing CABG so someone could have their gallbladder out. Then came perioperative beta-blocker therapy which demonstrated that many patients considered at risk would do well on such therapy. The Coronary Artery Revascularization Prophylaxis (CARP) trial showed that pre operative revascularization of stable CAD patients did not improve the outcome of major vascular surgery. However, there was a trend in CARP that favored revascularization for very high-risk patients. This hypothesis was tested in the current trial where only those with extensive stress-induced myocardial ischemia were randomized to revascularization or medical therapy alone. Although the trial was small (101 patients) the results were not encouraging that a larger study would demonstrate the value of revascularization. Thus, it will not likely be done.

The question now is where does this leave pre-operative testing? If revascularization does not make a difference, why look for ischemia? These studies did exclude those with significant left main stenosis, but we cannot justify cardiac catheterization in all stable patients for that reason. The only reason to delay surgery for cardiac catheterization would be for the unstable cardiac patient; those with unstable angina, resting ischemia, and stress tests done for symptoms that show high-risk features. Cardiac catheterization in stable or asymptomatic patients — whatever their risk profile — would seem unjustified.

Another interesting feature of this trial is that delaying surgery for cardiac revascularization lead to death from ruptured aneurysms for 2 patients (4%). So the urgency of the surgical situation needs to be considered. Also, aspirin and clopidogrel were not stopped for vascular surgery after coronary stenting and there was no difference between those on these drugs and those not in bleeding complications. We have to ask our surgeons to rise to the occasion as they do in Europe and Brazil. Almost half the patients in this study had significantly reduced left ventricular ejection fraction. Although this is a legitimate indication for cardiac catheterization if ischemic heart disease is the suspected cause, this study would suggest that this does not have to be done before vascular surgery if the patient is stable. For those interested, the implications of this study are consistent with the ACC/AHA Guidelines. So, experienced clinicians knew these things before this study was done. ■

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Questions & Comments

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Coronary Calcification and Perfusion Imaging

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Ramakrishna, G, et al. Relationship and prognostic value of coronary artery calcification by electron beam computed tomography to stress-induced ischemia by single photon emission computed tomography. *Am Heart J* 2007;153:807-814.

After a positive coronary CT scan, patients often undergo stress myocardial perfusion scanning, but the relationship between these two tests in relation to prognosis is poorly understood. Thus, these investigators from the Mayo Clinic identified 1230 patients who had undergone electron beam computerized tomography (EBCT) and stress single photon emission computed tomography (SPECT) within 3 months, over a 4-year period. After excluding patients with known coronary artery disease (CAD), valvular disease and paced rhythm or left bundle branch block the final population was 835 who consented to participate. They were followed for an average of 5 years to assess the primary endpoint of all-cause mortality. The secondary endpoints were myocardial infarction and coronary

revascularization after 3 months post testing. Coronary calcium was scored as normal (0), minimal (1-10), mild (11-100), moderate (100-400) and severe (>400). SPECT results were similarly categorized using the Cedars Sinai criteria.

Results: EBCT scores tended toward more abnormal studies (26% >400), whereas, SPECT scores tended toward low-risk studies (64% were normal). There was a weak correlation between the 2 studies; 4% of patients with a normal EBCT and 18% with an EBCT score >400 had a high-risk SPECT. Conversely, 70% of patients with EBCT >400 had a normal SPECT. EBCT better predicted a high-risk perfusion scan than any clinical variable. Adverse outcomes were correlated with both tests, but only EBCT predicted mortality in asymptomatic patients. The highest of mortality was in those with an EBCT >400 and a high-risk perfusion study. The authors concluded that EBCT and SPECT are weakly correlated; both predict mortality in symptomatic patients; but only EBCT predicts mortality in asymptomatic patients.

COMMENTARY

Interestingly, I am seeing patients referred because of an abnormal coronary calcium score on fast CT imaging ordered by their primary care doctor or by themselves. It is difficult not to perform a stress test on these patients, since they and their doctors are concerned about the results. This report of the Mayo Clinic experience in patients who have had both tests performed provides some interesting insights that may be of value in managing such patients. First, 96% of their patients with a calcium scan of zero had a negative SPECT. We are not told if the 4% with positive SPECT are true positives, but I suspect most were false positives. Second, even among those with a calcium score >400, 70% had a negative SPECT. These results are not different from other reports in the literature.

Unique to this study was the outcome of patients with a high-risk SPECT and a calcium score >400. They had a 10-year mortality of 42%. This is much higher than a calcium score of >400 alone of 27% and a high-risk SPECT alone of 31%. High-risk SPECT or calcium scans predicted higher mortality and morbidity in symptomatic patients, but only EBCT predicted outcomes in asymptomatic patients. However, the death rate in asymptomatic patients was 0.4% over 5 years. It is difficult to imagine that any testing or treatment strategy could be shown to reduce this low mortality.

This study has several limitations. It is retrospective. There is a referral bias toward patients with abnormal tests and 20% of their patients were lost to follow-up. Regardless, there are clinical implications to note. It is hard to imagine what benefit an asymptomatic patient derives from either test. Also, in patients with a markedly positive calcium scan, stress SPECT is usually negative. Therefore, it would seem that one could be selective in whom with a positive calcium score to do a stress test. Certainly symptomatic patients, but there would have to be other compelling reasons in an asymptomatic patient, given their excellent prognosis. ■

Transvenous Defibrillation Lead Defects in ICDs

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: Kleemann T, et al. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of >10 years. *Circulation* 2007; 115:2474-2480

KLEEMANN AND HIS COLLEAGUES FROM Ludwigshafen, Germany, report on survival of transvenous defibrillation leads during long-term follow-up. A total of 990 consecutive patients who received transvenous ICD defibrillation leads were included in this report. A spectrum of lead models from five different manufacturers was included, but most leads were manufactured by either St. Jude Medical or Medtronic.

Most of the transvenous leads were implanted using a subclavian puncture approach. Patients visited a defibrillator outpatient clinic every three months. At the time of the clinic visit, the ICD was interrogated and intracardiac real-time electrograms, pacing and sensing thresholds, lead impedance values, and stored electrograms were analyzed. Routine defibrillation threshold testing was not performed during follow-up. A lead defect was defined as "severe lead failure" if it required surgical intervention. This included failures that resulted in oversensing, lead impedance rises or falls, fractures, or abnormal electrical testing.

During a median follow-up of 934 days (interquartile range 368 to 1870) 15% of the 990 ICD leads failed. Patients with lead failures tended to be younger, more often female and had better preserved left ventricular

function. Actuarial analysis of lead survival showed survival rates at 5 years of 85% and at eight years of 60%. Of note, the annual failure rate increased over time. In the first four years after implant, failure, annual failure rates remained low in the 2% to 3% range. However, in the eighth, ninth and tenth years of follow-up, failure rates ranged from 11% to 20%.

The major lead complications included insulation defects (56%), lead fractures (12%), loss of ventricular capture (11%), abnormal lead impedance (10%), and sensing failure (10%). Insulation failure became more prominent over time accounting, for 70% of lead failures detected in leads older than 6 years. Newer leads did not show improved survival. In fact, there was a trend towards better lead survival in the first five years after implant with older model Medtronic 6936 and 6966 leads compared with a pooled group of models implanted from 1997 onwards. Lead defects became manifest either by inappropriate shocks (33% of patients) or by abnormal electrical testing during routine device evaluation (65% of patients). One lead failure was known to have occurred at the time of a spontaneous clinical cardiac arrest. In this case, the patient had to be resuscitated by external defibrillation. In the entire series, there were 207 deaths, but only 4 sudden deaths. In addition, 34 patients (3%) were lost to follow-up.

The authors concluded that transvenous ICD lead failure is a significant problem which becomes more prominent with longer lead implant durations. Careful long-term follow-up is required particularly in patients with longer implant durations.

COMMENTARY

In 2005, considerable attention was focused on the problem of ICD generator component failure. However, the failure rate for generators was quite low, even in the most severely affected models. Electrophysiologists have long known that the lead is the weakest part of an ICD system. However, unlike a generator failure where the failure may not become apparent until a critical time, lead failures often present with inappropriate shocks, or signs of dysfunction which can be picked up during a routine analysis. As a result, death due to lead failure is rare.

As we have shifted more to implants for primary prevention of sudden death and are implanting devices in younger patients with cardiomyopathy or inherited arrhythmia syndromes, the consequences of long-term lead deterioration will become more important. Lead extractions in very old leads can often be difficult and risky and associated with significant risk even in experienced hands. This is particularly true with defibrillator leads since they have two coils, one of which sits in the superior vena cava. With dual chamber or CRT devices, fibrosis between the other leads and this coil is common and the risk of vascular injury with extraction increases.

The data presented by Kleemann et al illustrate how important it is for manufacturers to seek better technology to improve lead longevity. Current ICD leads represent impressive technology, but continued research to enhance their long-term safety is needed. ■

Major Hemorrhage on Warfarin in Elderly Patients With Atrial Fibrillation

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Hylek EM, et al. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation* 2007;115:2689-2696.

RECENTLY, THE IMPORTANCE OF ANTICOAGULATION with warfarin in patients with atrial fibrillation and risk factors for stroke has been established in clinical trials and emphasized in recent guidelines. The major complication of anticoagulant therapy is bleeding and there is always a risk:benefit ratio which must be considered whenever warfarin is prescribed. In this paper, Hylek and her colleagues report an inception cohort study designed to define the rate of major hemorrhage in atrial fibrillation patients starting warfarin therapy. Patients were eligible for inclusion if they were over 65 years of age, had atrial fibrillation verified by an ECG and were starting warfarin therapy which would be managed by a single, onsite anticoagulation clinic. Patients were enrolled on the first day of warfarin and followed throughout the first year of therapy. The endpoints analyzed were: major hemorrhage, time to termination of warfarin and physician reasons for discontinuation. For this study, a hemorrhage was considered major if it was either fatal, required greater than or equal to 2 units of packed red blood cells or involved a critical site. Each patient was classified according to the CHADS2 scheme for known risk factors of stroke. Concurrent medications were obtained from electronic medical records. Use of over-the-counter agents such as aspirin or nonsteroidal anti-inflammatory drugs was also recorded.

The study cohort eventually included 472 patients. Of these, 47% were female and 54% were over 75 years of age with 153 patients (32%) over 80 years of age. With the use of the Outpatient Bleeding Risk Index, 95.3% were classified as intermediate risk and 4.7% as high risk for major hemorrhage with warfarin therapy. During the study, the following proportion of patient times were spent within the following INR ranges: 2.0 to 3.0 (58%), below 2.0 (29%), between 3.1 and 4.0 (11%), and 2% greater than or equal to 4.0.

During the first year after starting warfarin, major hemorrhages were noted in 26 patients (5.5%). These included: 9 intracranial hemorrhages, 11 gastrointestinal bleeds, 1 retroperitoneal bleed, 1 hemothorax after a fall, 1 ocular bleed, 1 hemarthrosis and 2 nose bleeds severe enough to require transfusions. The major hemorrhage rate was 7.2 per 100 person-years with a rate of intracranial hemorrhage of 2.5%. Increased age was associated with increased risk of bleeding. Patients 80 years of age or older had a bleeding rate of 13.1 per 100 person-years vs. 4.75 for those under age 80. Several risk factors for hemorrhage were identified: INR range greater than or equal to 4, older age, and first 90 days after initiation of therapy. During the first year of therapy, warfarin was discontinued in 134 patients. Although perceived maintenance of sinus rhythm was the most common cause (65 patients), safety concerns led to discontinuation in many others, particularly in those 80 or older. There was a strong correlation between bleeding risk and an elevated CHADS2 score demonstrating an important overlap between risks for bleeding and stroke.

The authors conclude that in general clinical practice, the risk of bleeding may be higher than has been estimated from prior randomized trials. These observations indicate that stroke prevention among the highest risk patients remains a challenge.

COMMENTARY

Stroke is the most serious complication of atrial fibrillation. Randomized clinical trials have clearly shown that warfarin decreases this risk by about 67% in an intention-to-treat analysis and has an even greater effect in an on-therapy analysis. However, many of the patients studied in these trials had already tolerated warfarin for some period of time before enrollment and patients thought to be at particularly high risk of bleeding were excluded. For some studies, this was more than 35% of the patients screened for participation. As a result, the annual rates of major bleeding were relatively low (1.4% to 4.2%) in these trials and in some other large scale trials in atrial fibrillation. In this paper, Hylek et al. show that "real world" anticoagulation of elderly patients with atrial fibrillation is still a major clinical problem. By studying an inception cohort, they mimicked the situation when a clinician makes a decision to start warfarin therapy. Even though all patients were followed systematically by an experienced anticoagulation clinic, the major hemorrhage rate in the first year of therapy was 7.2% and much higher in those patients 80 years of age or older. An important observation was the risk factors for stroke and for bleeding overlap, making clinical decisions even more difficult.

How should clinicians react to these data? Clearly both stroke risk and bleeding risk must be considered before starting anticoagulation. The need for concomitant drugs that might increase bleeding risk (eg, aspirin, anti-inflammatory drugs, other platelet inhibitors) must be evaluated at each visit and, in many cases, these drugs should be discontinued. Very careful monitoring to prevent excessive anticoagulation is needed especially in patients over 80.

Prognosis of Normal Coronary Arteries

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Palmeri S, et al. Late Angiographic Follow-up in Adults with Angiographic Normal or Minimally Narrowed Coronary Arteries. *Am J Cardiol* 2007;99:1374-1377.

Up to 20% of patients undergoing coronary angiography have normal arteries or mild luminal irregularities. I am often asked how long a negative coronary angiogram is good for before you have to consider repeating the test because of symptoms suggesting ischemic heart disease? This study from the Robert Wood Johnson Medical School in New Jersey sheds some light on this question. The investigators retrospectively reviewed 733 patients who had cardiac catheterizations done in the late 1980s and found 115 who had a second study in the ensuing 15 years (mean 9 years). Their angiograms were mixed with those from 20 patients reported to have luminal irregularities and reread blindly. Those with confounding conditions were excluded leaving a study population of 62 patients; 46 with normal arteries and 16 with lesions with < 30% narrowing. Most cardiac catheterizations were done for chest pain.

Results: Coronary artery disease (CAD) progression was more common in the luminal irregularity group

(81%) vs the normal arteries (41%). Acute myocardial infarction developed in 11% of patients with normal arteries. Overall, patients with normal coronary arteries progressed by -2.6% luminal diameter per year. Those with luminal irregularities progressed at -6% per year. The authors concluded that in patients with angiographically normal or near normal coronary arteries, short-term prognosis is excellent, but late CAD manifestation can occur.

COMMENTARY

Prior studies that followed patients with normal coronary arteries found such low event rates that we were lead to believe that they had an excellent 10-year prognosis. So, I used to teach that the warranty on a normal coronary angiogram was 10 years. Of course, there are exceptions to everything, so patients with compelling chest pain symptoms and a prior normal angiogram, should still be taken seriously. This study sheds further light on the issue because of the availability of repeat angiograms. Not surprisingly, patients with mild luminal irregularities often (80%) showed progression at a rate of about 6% of diameter loss per year. At this rate you could go from 30% to over 50% stenosis in less than 3 years. These patients have atherosclerosis and should be medically treated aggressively. In those with normal arteries by angiography progression of any underlying CAD is slower, so to get from zero to 50% narrowing could take 15-20 years. So, if the angiogram is stone cold normal the old impression that they are good for at least 10 years is probably still true. However, myocardial infarction often occurs because of rupture of a non-flow limiting plaque (<50% stenosis). In this study 11% of those with normal coronary arteries had a subsequent myocardial infarction. Thus, those with risk factors for CAD should have them addressed, since de novo or progression of angiographically silent CAD can occur late.

MAC and Aortic Atheroma in Stroke

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Karas MG, et al. Relation Between Mitral Annular Calcium and Complex Aortic Atheroma in Patients with Cerebral Ischemia Referred for Transesophageal Echocardiography. *Am J Cardiol*. 2007;999:1306-1311.

Although mitral annular calcium (MAC) is a risk for stroke, the mechanism is unclear. MAC is associated with complex proximal aorta (before the left subclavian) aorta atheromatous plaques and is seen in patients with risk factors for atherosclerosis. Thus, these investigators from New York explored the relationship between MAC and aortic atheroma (AA) in patients with cerebral ischemia. This was a retrospective cross-sectional study of patients referred for transesophageal echocardiography (TEE) to evaluate the source of cardioembolism over 6 years. Those with endocarditis, congenital heart disease or valvular disease were excluded. Complex plaques were those ≥ 4 mm in height or with mobile elements. The inclusion criteria were met by 419 patients; mean age 59; 47% women; and 24% with transient ischemic attacks. Patients with MAC were older (mean 72 years), were more likely to have traditional risk factors for coronary heart disease and had more previous cardiovascular events including atrial fibrillation. MAC patients had more carotid and intracranial atherosclerosis, especially in the ipsilateral cerebral territory. On echo MAC patients had more aortic valve calcium, left atrial enlargement, and left ventricular hypertrophy. MAC was associated with complex AA in the proximal aorta after adjustment for clinical and echo confounders. The severity of MAC was related to the incidence of complex AA. The authors concluded that MAC is associated with complex proximal aorta atheroma in patients with cerebral ischemia. These results suggest that proximal aorta complex atheroma are the cause of cerebral ischemia in patients with MAC.

COMMENTARY

Several studies have shown that MAC shares the same risk profile as atherosclerosis. Thus, it is not surprising that by focusing on patients with cerebral ischemic events that MAC would be associated with complex aortic atheroma and head and neck artery atherosclerosis. No patients in this study had evidence of thrombi on their MAC. It is reasonable then to presume that the reason MAC is associated with cerebral ischemic events is because it is a marker of proximal aorta and large-vessel head and neck complex atheroma, which are likely the cause of embolic events.

There are other possible confounders that accompany MAC such as left atrial enlargement, aortic valve calcification and diabetes. After correction for several clinical and echocardiographic variables, MAC was still associated with complex proximal AA. When patients with other possible causes of cerebral ischemia were excluded, the relationship between MAC and complex AA was strengthened. So the authors argued that the referral bias of only studying patients with cerebral ischemia suspected of having a cardiovascular etiology, actually strengthened the association between MAC and proximal AA

and buttresses the concept that aortic atheroma are the cause of cerebral ischemia in patients with MAC and no other discernable cause. Of course, this will need to be confirmed in a prospective study.

The practical implications of this study are that MAC is a strong marker of proximal aortic atheroma and aggressive risk factor modifications are indicated to prevent the development of complex plaques and subsequent stroke. ■

Pericardial Fluid Analysis: How Valuable Is It?

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Ben-Horin S, et al. Diagnostic Value of the Biochemical Composition of Pericardial Effusions in Patients Undergoing Pericardiocentesis. *Am J Cardiol*. 2007;99:1294-1297.

THE BIOCHEMICAL ANALYSIS OF PERICARDIAL FLUID is often done routinely, but there is little data on its value. Thus, these investigators from Israel retrospectively analyzed all pericardiocentesis patients over a 9-year period by chart review and phone calls. The causes of pericardial fluid were determined using standard diagnostic criteria, and idiopathic was defined when no cause was found over a 6-mnth or more follow-up. The study population consisted of 120 patients out of 173 who had biochemical studies and were followed for an average of 18 months. Patients with malignant effusions accounted for most of the mortality observed (41 of 59 deaths). Neoplastic effusions were more often bloody, but there was too much overlap with other causes to use this feature diagnostically. This was true for all biochemical tests as well. There were some findings that suggested a diagnosis. Bacterial effusions often had a low fluid-to- serum glucose ratio (0.3) and a low lymphocyte fraction (8%). The highest neutrophil counts were seen in patients with acute pericarditis (7.8), collagen vascular disease (7.5) and post pericardectomy (5.0). Only 2 of the 120 effusions could be classified as transudates based upon pleural fluid criteria using lactic dehydrogenase and protein levels. Also, no combination of tests accurately diagnosed any condition or group of like conditions. The authors concluded that almost all pericardial effusions are exudates and the measurement of -biochemical and cell count parameters is not useful for determining the cause of the effusion.

COMMENTARY

I am frequently asked by primary care doctors or other specialist to tap an asymptomatic pericardial effusion in order to make a diagnosis of the cause of the fluid accumulation. I have resisted these requests under the assumption that the risks of the procedure outweigh the diagnostic value. This article supports the general lack of value of pericardial fluid for etiologic diagnosis. However, the study is not definitive because of a number of problems. It is retrospective, so no specific protocol was used for pericardial effusion evaluation. In fact, 53 had no analysis done of their fluid and were excluded from the study. In these patients either the doctors involved had already made up their minds about the value of pericardial fluid analysis or they believed the diagnosis was obvious. A specific protocol, prospectively applied, may have performed better. The study population was small and dominated by 3 diagnoses (neoplastic 42, idiopathic 22, acute 17). The other 9 diagnoses had 10 patients or less in each diagnostic category. The results in the latter cases could be different if more patients were studied in each category. Some diagnoses could probably be inferred from other data such as uremic, traumatic and radiation. Finally, we are not given the reason for pericardiocentesis or the complication rate. Clearly the pleural fluid paradigm of transudate vs exudate does not apply to pericardial fluid. Was any measure of value? Perhaps percent lymphocytes which were markedly lower in bacterial pericarditis or collagen vascular disease, but there was too much overlap with other diagnoses to be definitive. In conclusion, pericardiocentesis should only be done for tamponade or impending tamponade and the fluid should only be sent or cell counts, culture and possibly glucose. ■

Coenzyme Q10 for Statin Myopathic Symptoms

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Caso, G, et al. Coenzyme Q10 on myopathic symptoms in patients treated with statins. *Am J Cardiol* 2007;99:1409-1412.

MILD MUSCLE SYMPTOMS OCCASIONALLY PREVENT some patients from taking statin drugs. Since blocking HMG-CoA also reduces coenzyme Q10 levels, Caso and colleagues hypothesized that the reductions in this essential component of muscle mitochondrial electron transport may impair muscle energy metabolism and con-

tribute to the muscle symptoms occasionally observed with statin therapy. Accordingly, coenzyme Q10 (CQ10) therapy may improve these symptoms and allow affected patients to stay on statins. The patient population was 32 patients with myopathic symptoms on statins and no other discernable cause. They were randomized to 100 mg of CQ10 or 400 units of vitamin E to control for the antioxidant effects of CQ10. The primary endpoint was a pain questionnaire done before and 30 days after treatment.

Results: In the CQ10 group, muscle pain severity decreased by 40% and pain interference with normal activities by 38%. There were no significant changes in these parameters in the control group (+9% and -11%, respectively). Plasma CK values were similar in both groups and were not altered by therapy. The authors concluded that CQ10 may decrease myopathic symptoms associated with statin use and allow more patients to benefit from these drugs.

COMMENTARY

In my experience it is not uncommon for patients to stop taking statins because of mild muscle symptoms (ache, stiffness, weakness, fatigue). CK is not elevated, so the exact cause of these symptoms is often unclear. The patients in this study were just such patients. Few had elevated CK and most had mild-to-moderate symptoms. CQ10 decreased symptoms in about 40%, suggesting that this may be an approach to increasing compliance with statins. Obviously, it won't work in everyone with these symptoms, probably because there is more than one reason for such symptoms.

Other studies have shown that statins can decrease CQ10 by 25 to 50%. Statins are known to decrease mitochondrial respiratory function and CQ10 is an essential cofactor for mitochondrial electron transport. Therefore, statin induced decreases in CQ10 could lead to muscle symptoms, which may be decreased by giving CQ10. Also, statins are known to increase blood lactate which as been observed in other mitochondrial disorders. So there seems to be a plausible biological basis for CQ10 therapy.

This study is small, so the observations should be confirmed in a larger group. Also, we have little mechanistic data since CQ10 and lactate were not measured. It was interesting that CK was unrelated to muscle symptoms or their change with CQ10. Thus, severe muscle damage was not likely a cause of these symptoms. This fits with the fact that rhabdomyolysis is a rare complication of statin therapy. Finally, only one dose of CQ10 was used. We do not know if higher or lower doses would be more or less effective. At this point it may be worth trying 100 mg of coenzyme Q10 for patients with mild-to-moderate myopathic symptoms on statins to see if compliance can be enhanced. ■

CME Questions

39. Which of the following is most true about pericardial effusions?
A. biochemical analysis can determine causation
B. almost all are exudates
C. the presence of blood is pathonomonic for neoplasm
D. bacterial pericarditis has a high glucose level

40. Mitral annular calcium is a harbinger of?
A. proximal aorta complex atheroma
B. intra and extra cranial atherosclerosis
C. cerebral ischemic events
D. all of the above

41. Which of the following is most true in patients with an EBCT coronary calcium score >400?
A. stress SPECT is normal in 70%
B. 10-year mortality is 70%
C. stress SPECT is high-risk in 2%
D. all of the above

42. Revascularization of patients with stress induced myocardial ischemia before major vascular surgery resulted in
A. lower mortality
B. fewer myocardial infarctions
C. less atrial fibrillation
D. no improvement in outcomes

43. Which of the following is most true about patients with normal coronary arteries undergoing a second coronary angiogram?
A. few had progressive atherosclerosis
B. about 10% developed acute myocardial infarction
C. myocardial bridging was found
D. coronary spasm was discovered

44. The risk of major hemorrhage in atrial fibrillation patients starting warfarin is?
A. nil
B. 25%
C. 7/100 person years
D. 2.5%

45. The incidence of long-term ICD lead failure is?
A. 5%
B. 10%
C. 15%
D. 20%

46. Coenzyme Q10 may be useful for?
A. decreasing statin induced myopathic symptoms
B. augmenting the LDL-cholesterol lowering effect of statins
C. increasing HDL-cholesterol
D. all of the above

Answers: 39.(b) 40.(d) 41.(a) 42.(d) 43.(b) 44.(c) 45.(c) 46.(a)

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1. present the latest information regarding diagnosis and treatment of cardiac disease;
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3. discuss the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and
4. present the current data regarding outpatient care of cardiac patients.

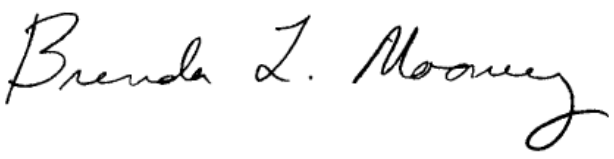
Each issue of your newsletter contains questions relating to the information provided in that issue. After reading the issue, answer the questions at the end of the issue to the best of your ability. You can then compare your answers with the correct answers provided in an answer key in the newsletter. If any of your answers were incorrect, please refer back to the source material to clarify any misunderstanding.

At the end of the semester, you will receive an evaluation form to complete and return in an envelope we will provide. Please make sure you sign the attestation verifying that you have completed the activity as designed. Once we have received your completed evaluation form, we will mail you a letter of credit. This activity is valid 24 months from the date of publication. The target audience for this activity is principal investigators and clinical trials nurses.

If you have any questions about the process, please call us at (800) 688-2421, or outside the U.S. at (404) 262-5476. You can also fax us at (800) 284-3291, or outside the U.S. at (404) 262-5525. You can also email us at: customerservice@ahcmedia.com.

On behalf of AHC Media, we thank you for your trust and look forward to a continuing education partnership.

Sincerely,



Brenda Mooney
Senior Vice-President/Group Publisher
AHC Media LLC

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.

Avandia, Risk of Congestive Heart Failure Significant Safety Risk

GlaxoSmithKline's rosiglitazone (Avandia) will receive a black box warning by the FDA because of concerns over heart failure associated with use of the drug. Pioglitazone (Actos) will also be subject to a black box warning for the same reason. The drugs, used for treatment of type 2 diabetes, have been scrutinized because of a recent meta-analysis that suggested that rosiglitazone was associated with a significant- increase risk of myocardial infarction and a borderline significant-increase risk of death from cardiovascular causes. (published www.NEJM. org on June 21, 2007 [10.1056/NEJMoa 072761]). Soon on the heels of the publication of this study, Glaxo rushed an interim analysis of its own trial to press. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial was published online in the *New England Journal of Medicine* on June 5, 2007. In the RECORD study, 4,447 patients with type 2 diabetes who had inadequate control with metformin or a sulfonylurea were randomized to receive add-on rosiglitazone or a combination of metformin and a sulfonylurea. The primary endpoint was hospitalization or death from cardiovascular causes. After mean follow-up of 3.75 years, 217 patients in the rosiglitazone group and 202 patients in the control group had the primary endpoint (hazard ratio 1.08), and after adding in pending primary end points the hazard ratio was 1.11 (95% CI, 0.93 to 1.32). There was no statistically significant difference between either group with regard to myocardial infarction or death from cardiovascular causes or any cause. There was a significantly higher rate of heart failure in rosiglitazone group (HR 2.15; 95% CI, 1.30 to 3.57). The authors conclude that the study was inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalization or death from cardiovascular causes, as there was no evidence of an increased death rate of cardiovascular causes or all causes associated with the drug, but there was a significantly higher rate of heart failure. There was insufficient data to determine if there was an increase risk of myocardial infarction (published at www.NEJM.org June 5, 2007 [10.1056/NEJMoa 073394]). The study was accompanied by 3 editorials that recommended caution in use of rosiglitazone and similar drugs especially in patients at risk for congestive heart failure. And while GlaxoSmithKline sees the study as vindication of the safety the drug, others, including the FDA, see the risk of congestive heart failure as a significant safety risk. Soon after publication of the RECORD study, a congressional hearing was held to discuss the safety of rosiglitazone and within days the FDA issued the black box requirement for rosiglitazone and pioglitazone. During the hearing, it came to

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, call: (404) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

light that at least one official at the FDA had suggested stronger warnings on rosiglitazone nearly a year ago, but her recommendation was ignored; she was reassigned and subsequently left the agency. Within several days of the rosiglitazone hearing, legislation was introduced to bolster the FDA's ability to monitor prescription drug side effects, a bill which also includes many of the Institute of Medicines recent recommendations on drug safety, and also included limiting direct-to-consumer advertising for newly approved medications.

Aspirin, Higher Doses No More Effective, Risky

What is the best dose of aspirin for prevention of cardiovascular disease? More than 50 million people take aspirin regularly in doses that range from 50 mg to over 1000 mg per day. The most commonly used doses are 81 mg and 325 mg per day. A recent systematic review of the English-language literature revealed that doses as low as 30 mg/day are effective at fully inhibiting platelet thromboxane production and preventing platelet aggregation. Despite this, higher doses are frequently used. The available evidence, primarily from secondary prevention trials, suggest that doses greater than 81 mg do not enhance efficacy, but do increase risk of GI bleeding and other toxicities. The authors conclude that aspirin doses of 75 mg to 81 mg/day are optimal for the indication of cardiovascular disease prevention, and higher doses are no more effective but are associated with higher risk (*JAMA* 2007; 297:2018-2024).

Subclinical Hypothyroidism Treatment Benefits

Subclinical hypothyroidism is defined as raised TSH levels with circulating thyroid hormones within the normal range. A new study suggests that treatment of subclinical hypothyroidism improves cardiovascular risk factors and quality of life. One hundred patients with a mean TSH of 6.6 mIU/l who had never received thyroid treatment and did not have cardiovascular disease were enrolled in a randomized, double-blinded crossover study of 100 µg of l-thyroxine or placebo daily for 12 weeks. Treatment with L-thyroxine reduced total cholesterol from an average of 231.6 to 220 mg/dl (P <0.001), LDL cholesterol from 142.9 to 131.3 mg/dl (P < 0.05), and waist to hip ratio from 0.83 to 0.81 (P < 0.006). Treatment also significantly improved endothelial function based on brachial artery flow mediated dilation, an early marker of atherosclerosis. Patients also reported decreased tiredness in the active treatment group, and there was a trend towards improvement in the perceived negative impact of hypothyroidism on sexual function. The authors conclude that treating subclinical hypothyroidism with l-thyroxine lead to significant improvements of cardiovascular risk factors and symptoms of tiredness (*J Clin Endocrinol Metab* 2007; 92:1715-1723).

FDA approvals

The FDA has approved a new transdermal patch for the treatment of early stage idiopathic Parkinson's disease. Rotigotine transdermal is a once-daily patch that is available in 2, 4 and 6 mg strengths. The drug is a dopamine agonist that affects D3/D2/D1 receptors and is thought to exert its effect via stimulation of dopamine D2 receptors. In clinical trials the patch was shown to improve scores on standardized rating scales for daily living and motor components in Parkinson's disease. The most common side effects are site reactions, dizziness, nausea, vomiting, somnolence and insomnia. Rotigotine transdermal will be available by the end of 2007 and will be marketed by Schwartz Pharma under the trade name Neupro.

The FDA has approved a new continuous contraceptive for women that is designed to eliminate menstruation. Wyeth pharmaceuticals Lybrel is a 28-day pill pack of levonorgestrel and ethinyl estradiol (90 µg/20 µg) that does not contain a placebo or pill-free interval. In clinical trials 59% of women achieved amenorrhea without bleeding or spotting, while 20% experienced spotting but did not require sanitary protection, and 21% required sanitary protection due to breakthrough bleeding. There was also no delay to return of menses after discontinuing the product nor any significant delay in fertility. Lybrel is scheduled to be available by July 2007.

Risedronate (Actonel) has received approval for a new once-a-month dosing schedule for the treatment of osteoporosis. The dose regimen requires patients to take 75 mg tablets on 2 consecutive days each month. The approval was based on a study that compared the monthly regimen with a daily regimen of 5 mg per day and showed no significant difference in efficacy for increasing bone mineral density at the lumbar spine, total hip, and hip trochanter. Risedronate is marketed by Procter & Gamble pharmaceuticals. ■