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CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

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INSIDE

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Antihypertensives and Central Aortic Pressure

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Williams B, et al. Differential Impact of Blood Pressure-Lowering Drugs on Central Aortic Pressure and Clinical Outcomes: Principal Results of the Conduit Artery Function Evaluation (CAFE) Study. *Circulation*. 2006;113:1213-1225.

THE OBSERVATION THAT BETA-BLOCKERS DO NOT REDUCE cardiovascular events as compared to other agents with equal blood pressure lowering in clinical trials may be due to different effects on central aortic pressure. Thus, a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the Conduit Artery Functional Evaluation (CAFE) study was conducted. The main objective of the CAFE study was to test this hypothesis. A second objective of CAFE was to evaluate the relationship between central aortic pressure and cardiac events.

ASCOT randomized patients 40 to 79 years of age with untreated or inadequately treated hypertension and at least 3 additional cardiovascular disease risk factors, including male sex, to atenolol plus thiazide or amlodipine plus perindopril as required. CAFE used radial artery tonometry pulse wave analysis to derive central aortic pressure. Of the 2199 ASCOT patients recruited for CAFE, 126 were excluded for inadequate pulse waveforms for analysis. The participants were largely white men (mean age, 63) with a mean pretreatment blood pressure of 160/93 mm Hg.

At the end of the study, brachial artery cuff pressures were similar and had decreased similarly (-26/-14 atenolol + thiazide vs -29/-16 mm Hg for amlodipine + perindopril). Derived central aortic pressure was reduced more by the amlodipine-based as compared to atenolol-based regimen (difference 4.3/1.4 mm Hg, $P < .001$). These differences were consistent throughout the study period. As expected, heart rate was significantly lower with the atenolol-based therapy. Central aortic pulse pressure was associated with a composite end point of total cardiovascular procedures/events and the development of renal dysfunction adjusted for baseline comorbidity ($P < .05$), as was peripheral pulse pressure ($P = .05$). Williams and colleagues

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concluded that different antihypertensive therapies may have different effects on central aortic pressure despite similar changes in brachial cuff blood pressure. Central aortic pulse pressure is related to cardiovascular outcomes, and may explain the different outcomes between the 2 treatment arms of ASCOT.

COMMENTARY

Over the years we have seen various theories advanced for picking one antihypertensive agent over another (eg, race, left ventricular hypertrophy regression), and now we have the affect on central aortic pressure. Smaller studies of shorter duration have shown that some antihypertensive drugs have less effect on central vs peripheral pressure, but this is the largest and longest duration study to document this. Also, the ASCOT study showed reduced cardiovascular events, including death and stroke, on amlodipine plus perindopril as compared to atenolol plus a thiazide. The central aortic pressure effect hypothesis is one potential explanation for this observation. However, the differences in central vs peripheral pressure in CAFE were small (4/1 mm Hg). Are these clinically significant?

The outcomes data in the CAFE study suggested that central aortic pulse pressure was predictive of a combined cardiovascular end point that included procedures and renal function, but so was peripheral pulse pressure. The CAFE subgroup did not establish that central pressures were more predictive of outcomes than peripheral pressures. Thus, the explanation for the differences in the ASCOT study were not proven to be the effects on central aortic pressure; but this hypothesis was not disproved because the subgroup was underpowered for outcomes. In addition, the fact that central pressures did correlate with outcomes keeps this hypothesis alive.

Recently, there has been much discussion about the lack of efficacy of beta-blockers for reducing cardiovascular outcomes in hypertensive patients. Also, beta-blockers have been shown to be less effective than other agents for reducing left ventricular hypertrophy and peripheral arterial medial thickness. In addition, brain natriuretic peptide levels are increased by beta-blockers vs reduced on other antihypertensives, suggesting that beta-blockers do not reduce central aortic and, hence, left ventricular systolic pressure as well. In the CAFE study, Williams et al suggest that heart rate reduction is the likely explanation for these differences. A slower heart rate allows reflected waves from the periphery time to augment the next systolic wave in the central aorta. The problem with this hypothesis is that a recent meta-analysis has shown that only studies using atenolol failed to show improved cardiovascular outcomes, but not those using metoprolol, yet both decrease heart rates. Perhaps the answer is that there is a problem with atenolol. If heart rate is the explanation, then other classes of drugs that lower heart rate (eg, diltiazem) should also be less effective. There is no data to support this. Thus, the mechanistic explanation for these results is still unclear.

There are several limitations to the CAFE study. The most important is that central aortic pressure was not measured, but derived from peripheral pulse waves. Apparently this method is well-validated, but for the non-physicist doubt lingers. Also, this is a substudy of a trial designed for other purposes, and bias could be introduced. The groups were well-matched and seemed to reflect the larger ASCOT study, but here were some baseline differences of unknown clinical significance. In addition, this was a relatively select patient population of largely older white men with moderate risk for coronary artery disease. Perhaps in such a group there is already some arterial stiffening that would augment differences between drugs on central aortic pressure.

At this point it may be prudent to reserve beta-blockers for hypertensive patients who need them for other reasons or for those who fail other agents, but don't be surprised if this rationale for picking one antihypertensive vs another also fades with time and more information. ■

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Exercise ECG Testing in Chest Pain Units

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *If a policy of invasive management is implemented for patients with positive exercise test results, the clinical risk score constitutes the main prognostic predictor of 1-year outcome.*

Source: Sanchis J, et al. Usefulness of Early Exercise Testing and Clinical Risk Score for Prognostic Evaluation in Chest Pain Units without Preexisting Evidence of Myocardial Ischemia. *Am J Cardiol*. 2006;97:633-635.

Controversy exists concerning the usefulness of stress testing for low-risk patients held for observation in a chest pain unit. Thus, this group from Barcelona, Spain, evaluated their experience with 340 consecutive patients held in an Emergency Department Chest Pain Unit for chest pain suspicious for angina, no ST segment deviation, normal troponins X2, the ability to exercise, and no prior evidence of ischemic heart disease using a clinical score vs standard ECG treadmill exercise testing (Bruce protocol). The clinical score was a simplification of the TIMI score, which considered age > 67 years, ≥ 2 episodes of chest pain in 24 hours, and the presence of diabetes. Each of these variables was given one point, so the maximum score was 3.

A negative stress test was found in 68%, and these patients were sent home. Those with a positive stress test (16%) were admitted and recommended for cardiac catheterization. In the 16% with inconclusive tests, clinical judgement resulted in the admission of 80% of them. The patients were then followed for one year, and the primary end point of all cause mortality and myocardial infarction assessed. Secondary end points included a composite of the above plus readmission for unstable angina. Of those hospitalized, 74% had cardiac catheterization and 48% were revascularized.

At one year, the primary end point was achieved in 7.4% of those with a positive stress test and 2.1% of the negatives ($P = .06$); the secondary end point was found in 9.3 vs 2.8%, respectfully, $P = .04$. The higher the clinical risk score, the more likely was a primary or secondary end point (0 to 12%; $P < .03$ for both). Among those with a positive or negative stress test, the clinical score further stratified their risk of an event (OR = 2.0; 95% CI =1.2-3.2; $P = .004$). Sanchis and colleagues concluded that in a protocol in which low risk chest pain patients with a positive exercise ECG test were referred for cardiac catheterization, a simple clinical risk score is the most powerful predictor of outcome at one year.

COMMENTARY

Perhaps the most interesting aspect of this study is the clinical risk score. It is a simplification of the TIMI score which eliminates the TIMI variables, which we now know makes a patient high risk (positive biomarkers, known coronary disease, ST transients). This simplified score which uses only historical factors is the most powerful predictor of one-year outcomes in this aggressive Chest Pain Unit protocol. Since 31% of those with a risk score of 3 had a negative stress test, yet 12% of those with a score of 3 had events, the study raises the question of whether those with a high score should be admitted and stress testing eliminated. This makes sense since clinical judgement should always trump testing, in my opinion. One difference between this study and others that may have come to different conclusions is that revascularization is a management strategy in this study, rather than an end point. This study builds on previous studies showing the value of certain strategies, and tests the relative value of a simple clinical assessment as compared to a testing driven strategy. Despite these protocol-driven constraints, simple clinical historical variables are still valuable. ■

Sudden Cardiac Death and Left Ventricular Systolic Dysfunction

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: *These findings support the aggressive development of alternative screening methods to enhance identification of patients at risk for sudden cardiac death.*

Source: Stecker EC, et al. Population-Based Analysis of Sudden Cardiac Death with and without Left Ventricular Systolic Dysfunction: Two-Year Findings from the Oregon Sudden Unexpected Death Study. *J Am Coll Cardiol*. 2006;47:1161-1166.

Stecker and colleagues report observations from the Oregon Sudden Unexpected Death

Study, which is an ongoing epidemiologic investigation of the characteristics of out-of-hospital sudden cardiac death. The study is being conducted in Multnomah County, Oregon (Portland and surrounding area).

In this report, the availability and significance of a pre-arrest assessment of left ventricular function is studied. Patients who experienced sudden cardiac death between Feb. 1, 2002 and Jan. 31, 2004 were evaluated. Resuscitated survivors of out-of hospital cardiac arrest were not included. Records for classifying the sudden death event were obtained from the county emergency medical response system, county medical examiners, and area hospitals. Prior medical records for the sudden cardiac death victims were then obtained from either these sources or from their primary care physicians.

Sudden cardiac death was defined as an unanticipated cardiac death within one hour of symptom onset. The study included unwitnessed sudden deaths in which patients were found dead within 24 hours of having been last seen alive and in a normal state of health. Patients with terminal noncardiac illnesses or identified non-cardiac etiologies for sudden death were excluded. The medical records were reviewed to see if they could contain a quantitative assessment of the patient's left ventricular ejection fraction (LVEF). The left ventricular ejection fractions were then categorized as either normal (greater than 55%), mildly to moderately reduced (36% to 54%), and severely reduced (less than or equal to 35%).

During the 2-year period included in this study, 714 residents of Multnomah County experienced an out-of hospital sudden cardiac death that satisfied study criteria. The mean age was 66 ± 19 years, and 60% were male. Medical records were available for review in 704 of 714 cases. Of these, only 121 cases (17%) had a prior assessment of left ventricular function before the sudden cardiac death event. Of these, in only 74 cases (63%) were the LVEF assessment conducted within 2 years of the cardiac arrest. Among the 121 patients for whom LVEF data were available, 58 patients had a normal LVEF, 27 had a mild to moderately reduced LVEF, and 36 had severely reduced LVEF. There were also 4 patients who had survived a prior cardiac arrest but had a normal LVEF and 2 patients with other cardiac conditions with a high risk for sudden death. Thus, based on current criteria for ICD implant, only 40 of the 121 patients would have been eligible for a primary prevention ICD implant.

Several interesting points about other clinical characteristics were noted. In the normal LVEF group, there were 8 patients (14%) who had a history of a seizure disorder. It could not be determined whether these arrests were precipitated by a seizure, were facilitated by anticonvulsant therapy, or were just an unrelated finding. Diabetes mellitus, hypertension, prior cerebrovascular accidents, and sleep apnea were found in reasonably equal proportions in the 3 LVEF groups. Left ventricular dysfunction was also significantly more prevalent among the 51 (42%) patients older than 75 years of age. Acute myocardial infarction or acute ischemia was a relatively uncommon finding. In only 7 cases was an acute MI recognized, nd 6 cases had pre-arrest ischemic symptoms. Other predisposing syndromes associated with sudden cardiac deaths were found in a few additional patients. Five patients had aortic stenosis, one patient had hypertrophic cardiomyopathy, and one patient had arrhythmogenic right ventricular cardiomyopathy that was diagnosed by other techniques.

Stecker and colleagues conclude that evaluation for left ventricular dysfunction before sudden cardiac death is uncommon. Even among those in whom an assessment of LV function had been obtained, left ventricular dysfunction is not common. Stecker et al encourage a renewed emphasis on identifying alternative sudden cardiac death risk predictors in the general population.

COMMENTARY

Strategies to prevent sudden cardiac death need to be broadly based. As illustrated in this study, a majority of sudden deaths occur in low-risk individuals. In low-risk individuals, expensive, toxic, or invasive therapies are impractical. The best method to prevent sudden death among low-risk individuals in the general population is to prevent or delay the development of acquired cardiac diseases that can lead to fatal arrhythmias. Despite this fact, individuals at much higher risk can be identified, and it is on such patients that current recommendations for ICD implantation are focused. What remains controversial is what level of baseline risk justifies proceeding to an ICD. Although the oldest and sickest patients are most likely to receive a shock after receiving an ICD, these patients also have higher mortality rates from nonarrhythmic causes, and the incremental gain in longevity may not be great. The data in this study indicate that nonspecific therapies that can be applied broadly may have greater value from a public health perspective than more complex interventions. ■

Physical Exertion, Exercise, and Sudden Cardiac Death in Women

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Synopsis: *These prospective data suggest that sudden cardiac death during exertion is an extremely rare event in women.*

Source: Whang W, et al. Physical Exertion, Exercise, and Sudden Cardiac Death in Women. *JAMA*. 2006;295: 1399-1403.

WHANG AND COLLEAGUES PERFORMED AN ANALYSIS of the relationship between acute physical exertion, routine exercise, and sudden cardiac death in women. Whang and colleagues analyzed data from the Nurses' Health Study. This is a large NIH-funded, longitudinal, epidemiologic study which involved over 120,000 female registered nurses who were between age 30 and 55 at the time of enrollment. The Nurses' Health Study began in 1976 and has provided important data about the epidemiology of cardiac and other diseases in women. For the purposes of this report, data from questionnaires obtained every 2 years about physical activity were collected. This information was then correlated with the occurrence of sudden cardiac death, defined as death within one hour of the onset of symptoms. For this study, most deaths during sleep were not counted as sudden deaths.

Among those who died suddenly, the medical records and reports from next of kin were analyzed, and the degree of physical exertion around the time of death was quantified on a scale of 1 to 8 metabolic equivalents. Moderate-to-vigorous exertion was estimated to be 5 or more metabolic equivalents. During the more recent years of the study, questionnaires included information about the average time spent in routine exercise counting lower intensity exercise, as well as moderate-to-vigorous activity. A number of different statistical methods were then used to analyze the relationship between chronic exertion and sudden death and the relative risk for sudden death during periods of high exertion. Proportional hazard models were used to adjust for other variables that might be related to sudden death. Patients who had a prior history of cardiac disease, stroke, or cancer prior to 1986 were excluded. This report covers approximately 79,000 women with data concerning their physical activities.

In this cohort, there were 288 sudden deaths that occurred over 1.93 million person years of follow-up. Of these, only 9 deaths occurred during an episode of moderate-to-vigorous exertion and, of these, only 3 were during voluntary exercise. The overall risk of a sudden death episode during moderate or vigorous exertion was estimated to be one per 36.5 million hours of exercise compared with an instance of one sudden death per 59.4 million hours with less or no exertion.

Using a case crossover analysis, the relative risk of sudden death during moderate-to-vigorous exertion was modestly elevated at 2.38 compared with risks at other time points. It was, however, noted that this slight elevation in risk was smaller and no longer significant among women who exercised 2 or more hours per week. Supporting this observation were data which indicated that women who reported exercising 4 or more hours per week had a lower absolute risk of sudden cardiac death. The trend indicating a protective effect of chronic exercise was still present, although of lower magnitude, even after multiple clinical factors which might affect the incidence of sudden death in the proportional hazards model.

Whang et al conclude that sudden cardiac during exertion is a rare event in women, and regular exercise for at least 4 hours per week can significantly minimize overall risk of sudden death.

COMMENTARY

There has been much interest in the role of exercise as both a trigger and a predictive factor for sudden death. This paper from the Nurses' Health Study supports previous data observed in men. Although there is an increase in the relative risk for death during exercise, the risk is low and chronic regular exercise serves to protect patients from this risk. Therefore, even though death may occur during exercise, patients should be encouraged to exercise on a regular basis. Routine exercise seems to be protective. ■

More About Plaques

ABSTRACTS & 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: *Although patients with SVG plaque ruptures are older and have more co-morbidities, the clinical presentation and angiographic and IVUS features are remarkably similar to those of native artery plaque ruptures. Also, MDCT "may be used to characterize coronary atherosclerotic plague morphology."*

Sources: Pregowski J, et al. Comparison of Ruptured Plaques in Native Coronary Arteries and in Saphenous Vein Grafts: An Intravascular Ultrasound Study. *Am J Cardiol*. 2006;97:593-597; Carrascosa PM, et al. Characterization of Coronary Atherosclerotic Plaques by Multidetector Computed Tomography. *Am J Cardiol*. 2006;97:598-602.

A GREAT DEAL OF INTEREST AND INVESTIGATION INTO the biology of vascular plaque has occurred over the past decade. It is now generally accepted that plaques are common, often throughout the coronary tree, and that many if not all may remain silent. It is also known that plaques can rupture or fissure, producing thrombus, and this may be a silent event, although often leading to the worsening of atherothrombosis. High quality coronary angiography has been the gold standard for identification of plaques, particularly so-called vulnerable or ruptured plaque. We have learned that in the presence of an acute coronary syndrome, presumably related to plaque rupture or erosion, there are often other plaques in the same coronary artery or in other arteries which are active and vulnerable. Importantly, the recognition that a relatively modest or non-obstructive narrowing in a coronary vessel may produce a fatal or non-fatal myocardial infarction has contributed to the great interest in plaque biology.

Two reports in the March 1, 2006, issue of the *American Journal of Cardiology* contribute to our knowledge of plaques. Pregowski and colleagues investigated the appearance of ruptured plaques in coronary arteries and saphenous vein grafts (SVG) using intravascular ultrasound (IVUS); the goal was to determine if there are significant differences between these sites of plaque formation. They studied 95 plaque ruptures within 76 SVGs in 73 patients, and visually compared the SVG ruptured plaques to a cohort of native coronary artery events matched for mean reference lumen area. While coronary plaque ruptures were located in the proximal or mid segments of the parent artery, SVG ruptures were noted at any site in a saphenous vein. Angiographic features that were tabulated included ulceration, intimal flap formation, lumen irregularity, or aneurysm. Coronary lesions were classified as simple in nature if there were no complex features. A standard IVUS pullback was performed in both groups. Plaque rupture was defined as a cavity that communicated with lumen, with an overlying fragment of residual fibrous cap. Deposits of calcium and increased or decreased brightness of the plaque (hyperechoic or hypoechoic plaque) were noted. Thrombus was found in the coronary arteries, but not in the SVGs. Eccentricity and remodeling characteristics were identified.

The results indicate that patients who had a ruptured SVG plaque were older and more often had major coronary risk factors. Of note, anginal symptoms were similar in the 2 groups, with 70% of patients presenting with an acute coronary syndrome. The mean SVG graft age was 12 years ± 5 years. Angiographic analysis defined over 90% of all ruptured plaques as complex, with a visible intimal flap far more commonly seen in the ruptured SVG. Otherwise, the features were similar. Grade 3 TIMI flow was present in all imaged SVG and native vessels before percutaneous intervention. The IVUS comparisons between the 2 groups demonstrated longer lesion lengths in the native coronary arteries, but comparable ruptured plaque and plaque cavity length. Minimal lumen area was found at the maximum plaque cavity site in half of the SVG ruptures, but only 30% of the native artery ruptures. In addition, distal lumen areas at the site of maximal plaque cavity were larger in the SVG lesions than in the coronary lesions. More than 70% of both groups demonstrated positive arterial remodeling. Calcium deposition and the frequency of eccentric lesions were similar. The site of initial rupture could be identified in approximately 60% in both groups; the rupture typically appeared at the shoulder of the plaque in 2/3 of all patients. Additional ruptures were noted in 40% of SVG lesions and 20% of native plaque patients; 5 patients had 2 additional native ruptures.

Pregowski et al conclude that the clinical, angiographic, and IVUS data support comparable complex angiographic appearances with similar IVUS features (the latter including positive remodeling,

eccentricity, shoulder rupture, etc). Clinical presentations were similar between the 2 groups; most patients presented with an acute coronary syndrome, with the culprit lesion more likely to be located in the SVG rather than a native coronary artery.

The data are consistent with other studies indicating that both native arteries and SVGs often undergo plaque rupture or erosion with subsequent thrombus formation in SVGs, as well as native vessels. Other reports using angioscopy and coronary angiography have also suggested a similarity between ulcerated plaques in native arteries and SVGs. In the present study, comparable features of atherosclerotic plaque and similar degrees of positive remodeling, eccentricity, and calcium deposition, suggest "that the mechanisms of plaque ruptures in native arteries and SVGs may also be similar." The SVGs tended to have larger reference plaque area, suggesting that "the atherosclerotic process is more diffuse in vein grafts than native arteries."

Another investigation of coronary plaque is a report of multi-detector computer tomography (MDCT) in the characterization of coronary plaque (Carrascosa, et al.). In this study, 40 patients were subjected both to MDCT and IVUS studies. All had documented coronary disease with > 50% lesion severity and were stable. Phillips 4 row multi-detector computed tomography was utilized, as well as IVUS, which was performed within 3 days of the CT evaluation. Multiple cross-sectional images were generated at 10 mm increments from the coronary ostia to the most distal segment. Digital coronary angiographic studies were performed using interventional techniques. IVUS pull-back was used in all subjects. The data sets of cross-sectional images from the MDCT and IVUS were matched according to the distance from the coronary ostia to be certain the same segments in plaques were evaluated.

A separate analysis of the MDCT and IVUS images were made by 2 independent investigators for the determination of obstructive coronary atherosclerosis. Percent luminal diameter was calculated for both techniques. Plaques were classified as soft, fibrous, or calcified. Percent decreases in luminal area for each segment were independently determined by both IVUS and MDCT; IVUS was considered to be the gold-standard. Overall, 194 segments were reviewed in 71 vessels. Obstructive coronary disease was found in 50 segments by IVUS, and in 57 by MDCT. Sensitivity for MDCT was 86% and specificity was 90%. Correlation between the methods was 0.78 to 0.87 for observer 1, $P < 0.0001$, and 0.83 to 0.92 for the second investigator, $P < 0.0001$. Inter-observer agreement for detection of obstructive coronary disease was good.

Overall, 276 plaques were observed by both techniques. The large majority were soft plaques with a relatively small percentage of fibrous and calcified plaques. MDCT showed excellent discrimination between calcified and non-calcified plaques, as well as "significant discrimination between fibrous and soft plaques." Pregowski et al conclude that their results are similar to other MDCT reports using coronary angiography as a comparator. They conclude that MDCT "may be used to characterize coronary atherosclerotic plaque morphology." They also stress that this technique can "in most cases" further differentiate soft from fibrous plaque. They conclude that "MDCT may provide unique, non-invasive, valuable information. . .to predict patients at risk for developing acute coronary syndrome." They suggest that MRI and contrast ultrasound may be useful, but have "limited spatial resolution for smaller vessels, such as coronary arteries." Finally, they predict that newer generation multi-detector computer tomography (> 16 slices) will result in improved image quality and a greater ability to identify soft from fibrous plaques.

COMMENTARY

There are no surprises in these 2 articles, both of which contribute to our knowledge of coronary plaque behavior, and stress the importance of being able to differentiate plaque characteristics in stable, as well as unstable individuals. The SVG study is of particular interest in that it documents the morphology and behavior of plaque rupture within venous grafts, which appear to be very similar to that which occurs in coronary arteries. This certainly suggests that preventive approaches, particularly extremely aggressive lipid lowering, should be beneficial in maintaining the health of SVGs. The Coronary Bypass Graft lovastatin trial of many years ago suggested that those individuals who achieved the lowest LDL levels had the least amount of graft disease. Little data are available regarding the role of newer statins in SVGs; the current publication strongly suggests that plaque behavior is comparable between diseased coronary arteries and diseased bypass grafts, with plaque rupture features being very similar. Thus, individuals who have had previous bypass grafting with saphenous veins should be treated to the same LDL targets as individuals who have acute coronary syndrome. I suggest that this target should

be as low as 70 mg/dL. It would be of considerable interest to see an analysis of long-term results of bypass grafting with respect to lipid levels, comparing individuals who have not been well controlled to those who have had excellent lipid profiles for over a period of 10 or more years.

The MDCT study is already outdated with respect to the advances in the field of imaging. Nevertheless, the ability of MDCT to characterize plaques as soft or fibrous, as well as being able to potentially identify vulnerable vs stable plaques certainly contributes to the Holy Grail today. Cardiologists are increasingly learning about the new imaging and, although many problems remain (see the April 2006 issue of *Clinical Cardiology Alert*), it is seems that non-invasive imaging of the coronary arteries has become big business. It remains unclear as to the clinical implications of MDCT being able to identify soft, fibrous, or calcified plaque. It will be important in future studies to see whether there are clinical outcomes differences with the different kinds of plaque identified by CT or other techniques, such that different therapies might be employed. The goal of this particular study was not to compare techniques with respect to the degree of coronary obstruction, but rather to characterize the nature of coronary plaque. This is an important and active area of current research; more to come! ■

CME Questions

25. Saphenous vein vs native artery plaques:
a. have similar characteristics.
b. SVG plaque has more calcium.
c. SVG plaques have more cholesterol gruel.
d. SVG plaques are less extensive.

26. Exercise in women:
a. increases the relative risk of sudden death.
b. reduces the overall risk of sudden death.
c. has no effect on sudden death.
d. a and b

27. In sudden cardiac death victims:
a. acute MI was common.
b. prior LV dysfunction is common.
c. pre-evaluation of LV function is uncommon.
d. a and c

28. Atenolol vs amlodipine for hypertension:
a. both reduce peripheral BP similarly.
b. amlodipine reduces central BP more.
c. central BP is also related to outcomes.
d. All of the above

29. Exercise testing in chest pain unit patients:
a. is superior to clinical evaluation for predicting outcomes.
b. is inferior to clinical factors for predicting outcomes.
c. identifies high risk patients for catheterization.
d. b and c

Answers: 25. (a); 26. (d); 27. (c); 28. (d); 29. (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. ■

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Reversal of Atherosclerosis Via Intensive Statin Therapy

Aggressive LDL lowering with statins, so-called "very intensive statin therapy," leads to reversal of coronary atherosclerosis, according to a new study. The ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial, a perspective, open label, blinded end-points trial, utilized the potent statin rosuvastatin in evaluating whether very intensive statin therapy resulting in LDL cholesterols in the low 60s associated with increases in HDL cholesterol could reverse atherosclerosis. Five hundred and seven patients were initially evaluated with intravascular ultrasound (IVUS) to determine baseline atheroma burden. Patients were then treated with intensive statin therapy with rosuvastatin 40 mg daily for 24 months, which resulted in an average LDL cholesterol of 60.8 mg/dL (mean reduction, 53.2%) and increased HDL cholesterol by 14.7%. IVUS was performed again at 24 months. The mean change in atheroma volume in the most diseased 10 mm sub segment was -6.1 (10.1) mm^3, with a median of -5.6 mm^3 ($P < .001$ vs baseline). Change in total atheroma volume showed a 6.8% median reduction. Adverse events were infrequent. Specifically there were no cases of rhabdomyolysis.

The authors conclude that lowering LDL-C to levels below currently accepted guidelines, when accompanied by significant increases HDL-C, can regress atherosclerosis in coronary disease patients, and is indicated for high-risk patients with established coronary disease (*JAMA*. 2006;295:1556-1565). An accompanying editorial notes that the study had several limitations, including lack of a control group or a comparator drug. They also note that the modest plaque reduction noted in this study "may not be the best measure of the treatment's effect on hard cardiovascular end points", however, they do applaud the pioneering work using intravascular ultrasound to help understand the anatomy and pathophysiology of coronary atherosclerosis and the effect of medical therapy on atheroma (*JAMA*. 2006;295:1583-1584).

Alternative Therapy for Depression?

Patients who fail SSRI treatment for depression may respond to an alternative medication, or the addition of a second medication, according to 2 studies in the March 23 *New England Journal of Medicine*. In the first study, 727 adults with a nonpsychotic major depressive disorder who had no remission of symptoms or could not tolerate the SSRI citalopram (Celexa) were randomized to receive sustained release bupropion

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(Wellbutrin) in a maximal daily dose of 400 mg, sertraline (Zoloft) at a maximum daily dose of 200 mg, or extended release venlafaxine (Effexor-XR) at a maximal daily dose of 375 mg for up to 14 weeks. The primary outcome was remission of symptoms based on the Hamilton Rating Scale of Depression (HRSD-17). Secondary outcomes included scores on the Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR-16). Remission rates, as assessed by the 2 scales, respectively, were bupropion - 21.3% and 25.5%, sertraline - 17.6% and 26.6%, venlafaxine - 24.8% and 25.0%. Response rates based on the QIDS-SR-16 were bupropion 26.1%, sertraline 26.7%, and venlafaxine 28.2%. There was no significant difference with respect to outcomes, tolerability, or adverse effects among the 3 drugs.

The authors conclude that after unsuccessful treatment with an SSRI, 1 in 4 patients have a remission after switching to another antidepressant, and all 3 drugs in the trial were reasonable choices (*N Engl J Med*. 2006;354:1231-1242). Another option for treating patients who failed treatment with citalopram was explored in the second study in the same issue. In the study, 565 adults who had a nonpsychotic major depressive disorder without remission after 12 weeks of citalopram therapy were randomized to receive add-on therapy with sustained release bupropion up to 400 mg per day, and 286 were randomized to receive buspirone (Buspar) at a dose of up to 60 mg per day. The same depression rating scales were used in this study as in the previous study. For bupropion and buspiron, respectively, HRSD-17 remission rate was 29.7% vs 30.1%, QIDS-SR-16 remission rate was 30.9% vs 32.9%, and QIDS-SR-16 response rate was 31.8% vs 26.9%. Bupropion was associated with a greater change in QIDS-SR-16 score, as well as the overall lower QIDS-SR-16 score at the end of the study and a lower dropout rate to due to intolerance (12.5% vs 20.6%, $P < 0.009$).

The authors conclude that the addition of bupropion or buspirone to citalopram is useful; however, the addition of bupropion may have some advantages, including a greater reduction in the severity of symptoms in fewer side effects (*N Engl J Med*. 2006;354:1243-1252).

FDA Actions

The FDA has approved the first generic HIV/AIDS drug for use in the United States. Zidovudine, manufactured under the trade name Retrovir by GlaxoSmithKline, was initially approved in 1987, and the company has had exclusive manufacturing rights until the drug's patent expired in September 2005. The generic is made by Aurobindo Pharma LTD of India. This is the same company that recently received approval from the FDA to co-package 3 antiretroviral drugs for the treatment of HIV/AIDS outside the United States. The regimen consists of lamivudine/zidovudine combination tablet along with efavirenz tablets. The co-packaging of these products has met the clinical safety, efficacy, and manufacturing quality standards required by the FDA. The approval is part of the Presidents Emergency Plan for offering full HIV treatment regimens for targeted areas of the world that are at risk to prevent HIV transmission and to treat AIDS and associated conditions. Patents and exclusivity prevent marketing of this combination in United States.

The FDA has approved a transdermal patch for the treatment of children with attention-deficit hyperactivity disorder. The patch delivers methylphenidate, the same ingredient found in Ritalin, in a daily patch that is applied early in the morning and removed 9 hours later. Methylphenidate patch is manufactured by Shire Pharmaceuticals and Noven Pharmaceuticals under the trade name Daytrana.

Salix pharmaceuticals has received approval to market a new tablet bowel prep for colon cleansing prior to colonoscopy. The virtually tasteless sodium phosphate tablets are an alternative to traditional liquid PEG bowel preps. The recommended dose is 32 tablets taken orally with a total of 2 quarts of clear liquids, administered as 4 tablets with 8 ounces of liquid every 15 minutes. Twenty tablets are given on the night prior to the procedure, with the remaining 12 tablets administered 3 to 5 hours prior to colonoscopy. Sodium phosphate tablets will be manufactured under the trade name OsmoPrep. ■