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CLINICAL CARDIOLOGY ALERT

A monthly update of developments in cardiovascular disease

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INSIDE

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Aliskiren and Valsartan for Hypertension

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Oparil S, et al. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. *Lancet* 2007;370:221-229.

ALISKIREN IS A NEW CLASS OF DRUGS THAT DIRECTLY INHIBIT renin and is approved in the U.S.A. for the treatment of hypertension. Valsartan is the best selling antihypertensive medication in the world. Little is known about the combination of these 2 drugs on blood pressure. Thus, Oparil and colleagues conducted a double-blind, placebo-controlled parallel group, dose escalation study at 312 centers in the U.S.A., Spain and Germany in 1797 patients with hypertension, but no severe cardiovascular disease. Patients were given once-daily oral aliskiren 150 mg or valsartan 160 mg or the combination or placebo for 4 weeks. Then they were force titrated to double the dose of each agent for 4 weeks. The primary end-point was a change in mean sitting diastolic blood pressure from baseline to week 8. Secondary end-points included systolic blood pressure measurements, the 4-week results and plasma levels of renin, renin activity and aldosterone. Overall 11% of the patients withdrew early from the study mostly because of inadequate blood pressure control. Premature discontinuation was least common in the combination therapy group and most common in the placebo group. Both mean sitting blood pressure and mean 24-hour ambulatory blood pressure decreased most on combination therapy and less but equally on both monotherapies. All 3 active drug groups decreased significantly vs placebo. Mean sitting systolic blood pressure decreased 4.6 mmHg on placebo, 13 mmHg on each monotherapy and 17.2 on combination therapy. Plasma renin levels were increased by all 3 active therapies, but most by aliskiren. Plasma renin activity was reduced by aliskiren alone or in combination, but was elevated by valsartan monotherapy. Aldosterone levels were not changed on aliskiren monotherapy, but were reduced by valsartan and combination therapy. Adverse events occurred in 2-3% of patients in each group. Potassium levels >5.5 mmol/L occurred in 2-4% of patients

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more in the combined therapy group. The authors concluded that the combination of aliskiren and valsartan in maximum recommended doses results in greater blood pressure lowering than does monotherapy with either agent in patients with hypertension. Also, combination therapy exhibited a low adverse event rate that was similar to monotherapy.

COMMENTARY

It is unusual to see pharmacologic treatment studies that combine maximum doses of 2 drugs. Most are done with less than maximum doses, leaving the question of what would happen if one drug was increased maximally, rather than adding another drug. The major rationale for using multiple drugs at low doses is to avoid adverse effects that may be seen at higher doses of one drug. This assumes that the added drug is from a different class of agents with a different adverse effect profile. Although this theory sounds good, it has never been convincingly proven in clinical trials. In fact, some studies have shown the opposite, that adverse effects tend to increase in frequency the more drugs you give. Thus, this study was interesting because all these issues were challenged. Maximum doses were used as monotherapy and in combination, and the 2 agents chosen had similar adverse-effect profiles. The results showed that combination therapy with aliskiren and valsartan was superior to monotherapy with either drug, with a similar adverse effect frequency.

One strength of the study was the use of an 8-hour ambulatory blood pressure recording to weed out the white coat hypertensives. This is important because they tend to get better over time, which results in greater placebo effects. Also, 24-hour ambulatory blood pressure measures were done and correlated well to the mean sitting blood pressure results. The major adverse effect observed was an increase in creatinine, which was seen in 4 patients on combination therapy (0.9%), 2 on valsartan, one on aliskiren and none on placebo. However, this was not accompanied by an increase in blood urea nitrogen and serum potassium levels > 5.5 mmol/L were not significantly different between the 4 groups (3% placebo, 2% aliskiren, 2% valsartan and 4% combination). None of these patients had events that lead to study drug discontinuation.

The biochemical results are also interesting. Plasma renin levels increased in all 3 therapeutic groups as might be expected from drugs that block its activity downstream. However, only aliskiren and combination therapy reduced renin activity. What if any effects elevated renin and renin activity have in patients on angiotensin receptor blockers (ARB) is unknown, but blocking renin's effect with aliskiren did further reduce blood pressure. Perhaps the observed inconsistent effect of adding an ARB to an ACE inhibitor on blood pressure is due to increased renin activity. Also, combination therapy and ARB monotherapy reduced aldosterone levels which would be expected to help reduce blood pressure. Thus, this may be an especially potent drug combination for favorably altering the renin angiotensin aldosterone system. ■

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Beta-Blockers for Asymptomatic Left Ventricular Systolic Dysfunction

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Colucci W, et al. Metoprolol reverses left ventricular remodeling in patients with asymptomatic systolic dysfunction. *Circulation*. 2007:116:49-56.

ASYMPTOMATIC INDIVIDUALS WITH SYSTOLIC LEFT ventricular (LV) dysfunction have an increased mortality. Angiotensin converting enzymes inhibitors (ACEI) and angiotensin receptor blockers (ARB) favor-

ably affect such patients, but little is known abut the effect of beta-blockers in this group. Thus, Colucci and coworkers hypothesized that beta-blockers would ameliorate LV remodeling in asymptomatic patients with LV systolic dysfunction and designed a randomized controlled trial, REversal of VEntricular Remodeling with Toprol-XL (REVERT) to test this hypothesis. Entry criteria included an LV ejection fraction (EF) < 40%, LV end-diastolic volume > 75 ml/m^2 no symptoms during ordinary activity for 2 months, and ACEI or ARB therapy for 3 months. Unstable patients or those with other significant morbidities were excluded. Of the 164 patients randomized, 149 had at least one dose of drug and a follow-up echocardiogram and constituted the modified intention-to-treat study population. The subjects were randomized into 3 groups: metoprolol extended release 200 mg/day; 50 mg/day; or placebo for 12 months. The primary endpoint was end-systolic volume index at 12 months.

Results: At 12 months there was a 14 mL/m^2 decrease in end-systolic volume index and a 6% increase in EF ($P < 0.05$ for both vs placebo) in the high-dose metoprolol group. Similar directional changes were observed in end-diastolic volume index, and with low-dose metoprolol and at 6 months, but they were not statistically different from placebo. Heart rate was significantly decreased by metoprolol, but blood pressure was not. The authors concluded that in asymptomatic patients with reduced LV systolic function, metoprolol ameliorates LV remodeling and improves systolic function.

COMMENTARY

The hypothesis chosen for this study is a surrogate endpoint for mortality and hospitalization for heart failure. In the MERIT-HF trial, symptomatic patients with heart failure due to systolic dysfunction treated with metoprolol exhibited improved survival and less hospitalizations vs placebo. An imaging sub-study showed reductions in LV volumes and an improvement in EF. Thus, the investigators in REVERT argue that similar changes in LV size and function seen in their study with metoprolol therapy in asymptomatic patients with LV systolic dysfunction would strongly support that mortality and morbidity would be reduced as well. They further argue that a large randomized trail to study metoprolol vs placebo in asymptomatic patients will not be done because of the large number of patients needed would make the cost prohibitive. They make a good point because despite an average EF of 27%, the death rate in REVERT was only 5% in 12 months. The implication is that asymptomatic patients with a low EF should receive beta-blockers. This is already recommended for post myocardial infarction patients with low EF. This study would extend such therapy to others with low EF.

Some might argue that the patients studied were similar to symptomatic patients because their definition of asymptomatic was no symptoms with ordinary activities. Their average BNP level was only 75 pg/Ml and only two-thirds were on any diuretic therapy. So, these were clearly different patients then those studied in MERIT-HF.

Another point worth noting was that 94% of their patients were on ACEI or ARBs, which are known to prolong life and reduce hospitalization in asymptomatic patients with systolic LV dysfunction. Thus, beneficial effects on LV remodeling in such a group seems more remarkable. Unfortunately, the patients were not studied again after stopping beta-blocker therapy to see if the effect persisted or was only present on therapy. Consequently, we have no idea how long to continue therapy if we elect to add beta-blockers to asymptomatic patients. Also, the effect seems dose related, since most endpoints were improved more on the higher doses of metoprolol. In addition, less patients in the high-dose group discontinued therapy because of adverse events. Thus, there is little downside to recommending beta-blockers for asymptomatic patients with LV systolic dysfunction. ■

Serial Biomarkers in Heart Failure

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Miller WL, et al. Serial biomarker measurements in ambulatory patients with chronic heart failure. *Circulation*. 2007;116:249-257.

BIOMARKERS SUCH AS BRAIN NATRIURETIC PEPTIDES (BNP) and troponin have been shown to be of diagnostic and prognostic value in patients with heart failure, but little is known abut the value of serial outpatient measurements. Thus, Miller and colleagues from the Mayo Clinic studied 200 outpatients with stable NYHA class III-IV heart failure every 3 months for 24 months. Patients awaiting transplant or revascularization and recently unstable patients were excluded. At each visit BNP and troponin T (TNT) were measured. The primary study endpoint was the time until death or transplantation. A secondary endpoint was time to first hos-

pitalization for decompensated heart failure. The goal of the study was to compare these endpoints over time to the biomarker measures. TNT above the upper limit of normal exhibited at 3.4-fold increase in the risk of an endpoint ($P < 0.02$). Further increases on serial measurements increased this risk to 5 fold ($P < 0.001$). A BNP greater than the 95% percentile in normal individuals increased risk 5 fold ($P < 0.001$), but further increases over time did not change risk. If both biomarkers were elevated, the risk increased to 8.6 fold ($P < 0.001$). However, once the TNT is > 0.03 mg/mL, then an elevated BNP does not add to the risk. The authors concluded that elevated TNT or BNP at any time during the outpatient follow-up of class III-IV heart failure patient predicts an increased risk of a cardiac event. Further increases in TNT augment this risk. The authors suggest that serial outpatient measurements of biomarkers contribute important information for the management of heart failure patients.

COMMENTARY

Biomarkers have proven useful for diagnosis, but their role in chronic disease management is less clear. Because of the challenge of determining fluid volume status in chronic heart failure patients, it was hoped that BNP measurements would aid in this clinical decision. In acutely decompensated patients, reductions in BNP appear to correlate with the improving condition of the patient, but what about the outpatient setting? This study would suggest BNP is of limited value. In their stable outpatients with moderate to severe heart failure, about two-thirds already had an elevated BNP (above 95th percentile for age and sex) and these patients did less well than those with normal values, but further increases in BNP did not predict events. Thus, BNP could be measured once in a stable outpatient to see if they are in a higher risk group, but serial measurements seem unjustified.

Surprisingly, TNT was predictive of a poor outcome and further rises predicted events and decreases predicted lower risk. About half of their patients had an elevated TNT at baseline (> 0.01 ng/mL) and 28% had values > 0.03 ng/L. The combination of an elevated BNP and TNT carried the greater risk of an event unless TNT was > 0.03 ng/mL. These results suggest that both BNP and TNT should be measured once in stable outpatients with moderate to severe heart failure and then consider re-measuring TNT if there is concern that the patient may be deteriorating. Further elevations in TNT may identify patients who should be listed for transplant.

Why does TNT predict events in stable outpatients with heart failure? It is unclear, but there are several possibilities. Perhaps TNT is measuring apoptosis of cardiac cells and when this accelerates the patient is worsening. Since most patients with heart failure have ischemic heart disease, perhaps TNT detects microinfarcts that herald worsening of heart failure. However, there did not seem to be a difference between patients with different etiologies and the predictive power of TNT, suggesting that worsening heart failure may be due to "heart failure infarcts" that are related to increased cytokines and inflammation.

Two caveats to the use of these biomarkers in heart failure patients: BNP is inversely related to body mass index and TNT is directly related to glomerular filtration rate. These factors have to be taken into consideration when evaluating the significance of single measurements. ■

ICDs for HCM

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: Maron BJ, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA* 2007;298(4):405-412.

This report describes a large group of patients with hypertrophic cardiomyopathy (HCM) who underwent implantable cardioverter defibrillator (ICD) implantation at 42 referral and nonreferral institutions in the United States, Europe and Australia. All HCM patients who received an ICD at participating institutions were followed in a registry and their outcome results are presented here.

The registry included 506 patients, who were aged 42 + 17 years at device implantation. One hundred and twenty-three patients received the devices for secondary prevention after episodes of ventricular tachycardia or cardiac arrest, while 383 patients thought to be at high risk received their ICD for primary prevention. The mean duration of follow-up was 3.7 years with a range of 1 to 16 years. Among the 506 study patients, 103 patients had one or more appropriate device terminations for either ventricular fibrillation (49) or ventricular tachycardia (54) during follow-up. The effective thera-

py was a defibrillation shock in 94 patients and overdrive pacing in 9, suggesting that most VT episodes were rapid with cycle lengths in the programmed ventricular fibrillation zone. The annual rate for appropriate interventions was 5.5% per year with a cumulative probability of appropriate intervention at 5 years of 23%. Among the 123 patients who had secondary prevention indications, 52 (42%) experienced appropriate ICD discharges during follow-up. This represented an appropriate intervention rate of 10.6% per year and a cumulative probability of appropriate discharge at 5 years of 39%. Among the 383 patients who received the device for primary prevention, 51 (13%) experienced an appropriate ICD discharge representing an annual intervention rate of 3.6% per year and a cumulative probability of discharge at 5 years of 17%.

Among the 103 patients with appropriate ICD therapies, 38 had a single appropriate intervention, 44 had 2 to 5 discharges, and 21 patients had more than 5 interventions. The time interval between ICD implant and the first appropriate discharge varied considerably and in 16 patients was between 5 and 10 years after insertion. The proportion whose first appropriate discharge occurred after 5 years was 27%. Age and gender did not affect the risk for appropriate ICD intervention and interventions were observed among patients taking all types of antiarrhythmic drugs. Of note, in the subgroup of patients who had interventions to relieve outflow tract obstruction, appropriate discharge rates were fourfold more common in patients with prior alcohol septal ablation (4 of 17, 24%) compared to patients who had previously undergone surgical septal myectomy (6 of 50, 12%). Combining various risk factors was not particularly helpful for grading prognosis is this group all of whom had at least one risk factor for sudden death . Twenty-four of the 173 (14%) patients with appropriate discharges had only one risk factor, 16 of 143 (11%) had 2 risk factors, and 10 of 59 (17%) had 3 or more risk factors. During the study period, 39 of 506 patients died and 10 underwent heart transplant. Nineteen of the 39 deaths were not directly related to their hypertrophic cardiomyopathy, but 20 died of either end-stage systolic dysfunction with advanced heart failure or embolic stroke. One final patient died with recurrent arrhythmia and an ICD malfunction.

Inappropriate shocks occurred in one-third of the patients; 132 patients who never received appropriate ICD intervention, as well as 34 patients who did receive an appropriate ICD intervention. Other major complications included infections (19 of 506, 3.8%), hemorrhage and thrombosis (8 of 506, 1.6%), and lead problems requiring intervention including fractures, dislodgement or oversensing (34 of the 506, 6.7%).

The authors conclude that an ICD effectively and reliably treats life-threatening ventricular arrhythmias in patients with hypertrophic cardiomyopathy. They believe their data argue that a single marker for high risk may justify consideration for a primary prevention ICD in patients with HCM.

COMMENTARY

ICD insertion for the primary prevention of sudden cardiac death in patients with HCM remains a controversial topic. This report expands on earlier data from this multicenter registry and confirms that ICD therapy is an effective approach to sudden death prevention in patients with HCM. The problem of risk assessment for cardiologists who encounter patients with HCM in the office is still significant. As acknowledged by the authors, referral centers, such as those that participated in this registry, collect higher risk patients than those seen in community-based surveys of patients with HCM. Clearly, the ICD is the appropriate strategy for secondary prevention but the rate of appropriate ICD usage in the primary prevention group is lower yet these patients are at the same risk for complications, including inappropriate shocks, lead complications and infections. It is still appropriate to discuss these issues with patients and make sure they understand both the risks and benefits of ICD therapy before proceeding with implantation. ■

Management of Ventricular Arrhythmias in ARVD/C

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Dalal D, et al. Long-term efficacy of catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Am Coll Cardiol* 2007;50:432-440.

Dalal and his colleagues describe data from the Johns Hopkins Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) registry concerning the efficacy of catheter ablation for ventricular tachycardia (VT) in this condition. Data were collected from multiple electrophysiology laboratories participating in the registry. The authors identified 24 registry participants who met the task force definition of ARVD/C and who had undergone one or more attempts

at radiofrequency ablation for recurrent ventricular tachycardia. The mean age at first procedure was 36 + 9 years and 46% of the patients were male. ICD implantation was performed in 5 (21%) of the patients before their first catheter ablation procedure, in 14 (58%) of the patients after one or more ablations, and 5 (21%) of the patients never received an ICD. Thirteen of the 14 patients underwent more than one ablation procedure because of recurrent VT after the initial ablation. More than 1 distinct VT morphology was induced during 77% of the procedures. VT mapping was performed using 3-dimensional mapping during 10 of the procedures and traditional entrainment or activation sequence maps were used in the others. Ablation procedures were either considered completely successful if there was no inducible VT after ablation (22 of 48 procedures , 46%), partially successful if the clinical VT was suppressed but other VT's could still be induced (15 of 48 procedures, 31%), and a procedural failure if the clinical VT was still inducible (11 of 48 procedures, 23%). There was one major complication related to an ablation procedure. One patient who was undergoing his third ablation attempt developed an unstable VT and then became severely hypotensive. Resuscitation was unsuccessful. There were no mechanical complications of the procedure.

During long-term follow-up, time to recurrence after each ablation attempt was calculated. The mean time to recurrence after each ablation was 8 + 10 months and VT recurred after 40 of the 47 (85%) ablations. Only one patient had a single RF ablation procedure that proved successful both short- and long-term. The cumulative VT recurrence for each survival after a single radiofrequency ablation procedure was 75% at 1.5 months, 50% at 5 months, and 25% at 14 months of follow-up. The cumulative incidence of VT recurrence after a single procedure was 64%, 75% and 91% at the end of 1, 2, and 3 years. Of interest, there was no significant difference in the VT recurrence rate based upon the presumed acute success of the procedure. There was also no difference in success rates related to whether or not 3-dimensional mapping was used to guide ablation.

The authors conclude that catheter ablation of VT in patients with ARVD/C is at best a palliative procedure designed to reduce the frequency of VT episodes. Further studies to refine techniques for ablating arrhythmias in this difficult condition need to be developed.

COMMENTARY

These data from the ARVD/C registry should be useful to cardiologists and electrophysiologists who care for patients with ARVD/C. This condition is caused by mutations in the genes that code a number of desmosomal proteins. Alterations in the structure of these proteins results in poor cell-to-cell adhesion and fibro-fatty degeneration in multiple areas of the right ventricle. These changes are progressive over time and frequently result in sustained and potentially life-threatening ventricular arrhythmias. Progression can occur at varying rates that are impossible to predict when the patient is first identified. Many patients with ARVD/C have frequent arrhythmias that are drug unresponsive and the frequent episodes of VT make ICD therapy problematic. This paper illustrates that ablation therapy also has significant limitations in patients with gradually progressive changes in the myocardial substrate for arrhythmia. However, despite the low overall success rate reported here, ablation can still be a useful adjunct in these patients as a way to decrease the frequency of ICD therapies. The operator and patient, however, should recognize that ablation is likely to provide only short-term palliation rather than a long-term solution to the problem. ■

Vulnerable Plaques by CT

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.

Source: Motoyama S, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol* 2007;50:319-326.

THE INCREASING USE OF 64-SLICE COMPUTED tomography or MSCT is beginning to significantly impact the medical literature. This study, from Japan; Irvine, California; and Gaithersburg, Maryland, is an early effort of utilizing MSCT to evaluate "vulnerable" coronary arteries that could cause an acute coronary syndrome (ACS).

Coronary Plaque Evaluation by MSCT: The authors suggest that a ruptured coronary plaque is likely to be very similar in composition to a vulnerable, but non-ruptured plaque that has yet to become eroded or rupture, and that such imaging signatures can be assessed using high-quality imaging technology to identify lesions that are at high risk for causing a subsequent coronary event. While interest in plaque composition and imaging is

very high at the present time, it remains unclear if current imaging capability allows for detection of a variety of important plaque characteristics. There are numerous catheter-based technologies and techniques being applied to help answer important questions relating to plaque vulnerability. These include optical coherence tomography, intravascular magnetic resonance, thermography, and most familiar, intravascular ultrasound or IVUS. The authors state, "Recent improvements in CT technology and the advent of multislice computed CT have spurred interest in non-invasive detection of morphologic characteristics of vulnerable plaques." This study began in 2004 with the utilization of 0.5mm X 16-slice CT; 56 of the 71 ACS patients enrolled had no further imaging; 15 individuals were added to the original cohort, resulting in a total of 71 patients; the latter group all had 64-slice imaging. The cohort was derived from screening of 441 patients. Individuals were classified as having stable or unstable angina, as well as acute coronary syndrome (ACS), which was defined by elevation of troponin or unstable angina pectoris. Stable angina patients with single vessel disease who had undergone a coronary angiogram were studied. STEMI patients were included if they were evaluated greater than 24 hours from the onset of chest pain and were symptom free. Coronary angiograms were used to identify the culprit lesion as well as to define other angiographic parameters. Of the 71 patients, 10 had STEMI, 9 had NSTEMI, 19 had unstable angina, and 33 had stable angina. Invasive procedures were performed on a majority of the patients. The MSCT protocol utilized is highly technical; readers interested in tomography details should refer to the article. Characteristics identified and analyzed include coronary artery remodeling (positive remodeling relates to increase in coronary artery diameter at a plaque site that is at least 10% larger than the adjacent reference segment). Plaques were analyzed by the presence or absence of calcification as well as IVUS analysis. Spotty and large calcifications were analyzed. Vessels were assessed as to presence of soft or fibrous plaque. Only patients imaged with the 64-slice unit were included for an IVUS analysis. Individuals who interpreted this study were blinded to clinical status. Sensitivity, specificity, positive/negative predictive values, and diagnostic accuracy were assessed for each vessel.

Results: All 71 patients had comparable baseline characteristics (age, gender, or presence of diabetes/hypertension/hyperlipidemia, smoking and obesity). Positive expansive remodeling was noted in the large majority of culprit lesions (87%). Spotty calcification was noted in 63%. Culprit lesions had a large lipid core, with calcification seen in 22%. Stable angina patients demonstrated a low likelihood of positive remodeling, and plaques characterized as soft. While spotty calcification was observed in 21%, larger calcium plaques were found in 55%. Remodeling was significantly greater in ACS lesions vs stable angina. Stable angina patients were much more likely to have large calcifications; most were unlikely to demonstrate positive remodeling. Spotty calcification was found in 2/3 of ACS lesions, whereas stable angina patients had spotty calcifications only 1/5 of the time. Positive remodeling demonstrated the best sensitivity, specificity, and predictive values; correlation with soft plaque and spotty calcification was common. Plaques that demonstrated positive remodeling, spotty calcification, and soft plaque by IVUS had a positive predictive value of being associated with an acute event of 95%.

The authors conclude that culprit legions in ACS show positive remodeling, plaque lesions with a significant lipid core; all characteristics not associated with stable angina. Positive remodeling was the most important predictor of a culprit lesion, as noted by many others. Such lesions were associated with lipid cores consisting of soft plaque or necrotic core. Nevertheless, the authors state "extreme caution should be exercised in labeling low attenuation… in a plaque as soft plaque or necrotic core." The authors suggest that IVUS imaging in evaluation of plaque as soft vs non-soft needs to be improved, and that 64-slice imaging is a better technique for identification of culprit legions. Presence of positive remodeling, soft plaque or obvious lipid, and spotty calcification are highly predictive of a causal ACS event, whereas absence of all 3 features had a very high negative predictive value. The authors suggest that characteristics consistent with a not yet disrupted vulnerable plaque are likely to be the site of a subsequent acute event. They point out that the plaque and necrotic core sizes are the most important determinants of plaque vulnerability. The larger the plaque extent and necrotic core size, the higher the likelihood of the plaque to rupture. Ruptured plaques that have disrupted and healed are highly likely to demonstrate narrowing of the cross-sectional area of > 50-75%.

Many plaques with a necrotic core occupy an extensive area. Plaque volume may be enormous "without compromising the lumen size to greater than 40%." This phenomena is related to positive outward remodeling, and confirms the widely observed phenomena that acute myocardial infarction often arises from a non-obstructive plaque. Pathological features of hemorrhage, large necrotic core, macrophage inflammation and calcification are characteristics of vascular remodeling. Such plaques are called TCFA or thin cap fibro-atheroma.

Stable plaques generally show no expansive remodeling and even negative shrinkage. The literature indicates that most TCFA occur in the proximal or mid-portion of a coronary artery and furthermore that "the number of vulnerable plaques present in any patient is small." These features make "an effort to detect vulnerable plaque justifiable." The authors suggest that individuals with a high-event likelihood i.e., > 20% over 10 years, "may constitute the most appropriate population to be subjected to MSCT for potential identification of vulnerable plaques." Thus, candidates for imaging with renal impairment, diabetes, or peripheral vascular disease should be considered for coronary imaging with MSCT. Identification of vulnerable plaque in such individuals "may place the subjects at a very high risk (probably in excess of 15%) of developing acute coronary events per year. This will be the key role for coronary imaging." The authors acknowledge that it is difficult to differentiate between thrombus or lipid-rich plaques from fibrous plaques just on the basis of plaque attenuation, as many lesions have complex pathologies. They acknowledge that the long-term implications of a vulnerable plaque identified by MSCT is unclear, and much more data will be needed. The authors appropriately suggest that more imaging will be seen as hospitals and cardiology groups acquire 64-slice imaging equipment.

COMMENTARY

It is clear that hospitals around the country are eagerly acquiring 64-slice CT units. It is not yet clear how accurate and reliable such imaging is for so-called vulnerable plaque. Limitations of this study included the small percentage of patients who underwent imaging analysis with a 64-slice unit, and the modest size of the series. This study, as well as others in the literature, is concordant with the view that stable vs unstable plaque characteristics within the coronary circulation may be predictive of vulnerable plaque and subsequent plaque rupture, and that features of fibrous or stable plaque as assessed by multi-slice CT may imply "protection" from acute plaque ruptures, although such vessels are likely to be implicated in chronic stable angina. We do not have specific therapies that differ for vulnerable plaque vs stable plaque; there is general acceptance that all patients with coronary disease, even if relatively low risk, should be treated vigorously with lipid lowering, aspirin, and perhaps beta blockers and ACE inhibitors. It is attractive to use the new powerful imaging techniques in clinical practice. If some of the technologies currently being tested in many centers including MSCT turn out to be valuable, this will change the focus of our efforts from treating the clinical event to even more aggressive prevention. ■

CME Questions

53. Serial outpatient measurements of which biomarker is of value in heart failure patients?
A. Troponin T
B. BNP
C. C-reactive protein
D. All of the above

54. Maximum doses of aliskiren and valsartan in hypertension
A. decrease plasma renin levels
B. increase plasma aldosterone levels
C. reduce blood pressure greater than monotherapy
D. increase the incidence of adverse effects

55. Beta-blockers are useful for treating
A. asymptomatic heart failure
B. symptomatic heart failure
C. acute decompensated heart failure
D. A and B

56. On CT imaging vulnerable plaques are characterized by
A. large amounts of calcium
B. positive remodeling
C. hard lipid core
D. all of the above

57. ICD for primary prevention in high-risk HCM patients results in
A. appropriate shocks in 3.6% per year
B. one-third having inappropriate shocks
C. greater than 5% having complications
D. all of the above

58. The management of ventricular arrhythmias in ARVD/C patients includes
A. antiarrhythmic drugs
B. RF ablation
C. ICD
D. all of the above

Answers: 53.(a) 54.(c) 55.(d) 56.(b) 57.(d) 58.(d)

CME Objectives

The objectives of Clinical Cardiology Alert are:

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

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

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

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

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.

Oral Anticoagulant + Antiplatelet Therapy = Danger

In this issue: *Adding an anticoagulant to aspirin is of no value in patients with peripheral artery disease, older adults with coronary disease benefit from aggressive statin therapy, simvastatin may reduce the risk of dementia and Parkinson's disease by as much as 50%, MiraLAX is safe for long-term use in patients with chronic constipation, the FDA greenlights Avandia, brings back Zelnorm for limited use, and recommends approving Evista for breast cancer prevention.*

Patients with peripheral artery disease are at high risk for cardiovascular complications. Antiplatelet drugs are routinely prescribed for these patients, but is adding an oral anticoagulant of value? No, according to a new study. In fact, the combination may be dangerous. More than 2,100 patients with PAD were randomly assigned to antiplatelet therapy with an oral anticoagulant or to antiplatelet therapy alone. The first coprimary outcome was myocardial infarction, stroke, or death from cardiovascular causes. The second coprimary outcome was myocardial infarction, stroke, severe ischemia of the peripheral or coronary arteries leading to urgent intervention or death from cardiovascular causes. After an average followup of 35 months, the first coprimary outcome occurred in 132 of 1080 patients receiving combination therapy (12.2%) and 144 of 1081 patients receiving antiplatelet therapy alone (13.3%) (RR 0.92; 95% CI, 0.73 to 1.16; $P = 0.48$). The second coprimary outcome occurred in 172 patients receiving combination therapy (15.9%) compared to 188 patients receiving antiplatelet therapy alone (17.4%) (RR 0.91; 95% CI, 0.74 to 1.12; $P = 0.37$). Life-threatening bleeding occurred in 43 patients receiving combination therapy (4.0%) as compared to 13 patients receiving antiplatelet therapy alone (1.2%) (RR 3.41; is 95% CI, 1.84 to 6.35; $P < 0.001$). The authors conclude that adding an oral anticoagulant to antiplatelet therapy in patients with PAD was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications, but was associated with an increase in life-threatening bleeding (*N Engl J Med* 2007; 357: 217-227). ■

High-Dose Statin Therapy, Value for Older Adults

Aggressive lipid lowering with high-dose statin therapy may be of value in older adults with stable coronary disease. The multicenter study from the United States included 3,809 patients 65 years or older with coronary artery disease and cholesterol levels less than 130 mg/dl who were randomized to receive atorvastatin 10 mg or 80 mg. Patients on low-dose atorvastatin achieved average cholesterol levels of 100 mg/dl versus 70 mg/dl for high dose therapy. The primary endpoint was occurrence of first major cardiovascular event such as death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal stroke. Patients treated with high-dose atorvastatin were found have a 2.3% absolute risk reduction and a 19% relative risk reduction for the primary endpoint (hazard ratio 0.81 [95% CI, 0.67 to 0.98]; $P = 0.032$). Mortality rates were

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lower for CHD, nonfatal non--procedure-related myocardial infarction, and stroke in the high-dose group. High-dose therapy was not associated with elevated creatine kinase levels. The authors conclude that treating older patients with coronary heart disease more aggressively to reduce low-density lipoprotein cholesterol levels provides additional clinical benefit (*Ann Int Med* 2007;147: 1-9). ■

Simvastatin, Best for Parkinson's Disease

Simvastatin, not atorvastatin or lovastatin, is associated with a dramatically reduced risk of dementia and Parkinson's disease (PD) according to a study from Boston University and VA database of 4.5 million individuals (95% men). In the observational study, over 700,000 subjects took simvastatin, nearly 54,000 took atorvastatin, and over 54,000 patients were prescribed lovastatin. Three models were used to evaluate the data, adjusting for covariates associated with dementia or Parkinson's disease. The first model was adjusted for age; the second model adjusted for 3 known risk factors for dementia: hypertension, cardiovascular disease, or diabetes; and the third model adjusted using the Charlson index, an index that provides broad assessment of chronic disease. Using the third model, the hazard ratio for dementia was 0.46 for simvastatin (CI 0.44-0.48, $P < 0.0001$) and 0.91 for atorvastatin (CI 0.80-1.02, $P = 0.11$). Lovastatin was not associated with a reduction in the incidence of dementia. The hazard ratio for newly acquired Parkinson's disease was 0.51 for simvastatin (CI 0.49-0.55, $P < 0.001$). There was no reduction in PD with atorvastatin or lovastatin. The degree of risk reduction utilizing the other models was similar with simvastatin. The authors conclude that simvastatin is associated with a strong reduction in the incidence of dementia and PD, while atorvastatin is associated with a modest reduction in incidence of dementia and Parkinson's disease that shows a trend toward significance (*BMC Med* published online July 19, 2007). The surprising finding suggests a difference between simvastatin and atorvastatin out of proportion to their cholesterol lowering effects, which the authors suggest may be due to the ability of simvastatin to cross the blood brain barrier more readily than other statins. ■

Polyethylene Glycol for Chronic Constipation

Long-term use of polyethylene glycol is safe and effective for chronic constipation according to the results of a new study from Alabama. More than 300 patients were randomized to receive polyethylene glycol 3350 (MiraLAX) in a single 17 g dose per day or placebo for 6 months. The primary endpoint of improvement of constipation on an objective scale was reached in 52% of the PEG patients and 11% placebo patients ($P < 0.001$). Similar efficacy was seen in a subgroup of 75 elderly patients. There were no significant adverse events other than diarrhea, flatulence and some nausea associated with PEG. The authors conclude that PEG laxative is safe and effective for use in patients with chronic constipation for up to 6 months (*Am J Gastroenterol* 2007;102:1436-1441). The study is particularly important because MiraLAX is now available over-the-counter and long-term use by patients with chronic constipation is likely. ■

FDA Actions

The FDA's Oncologic Drugs Advisory Committee, on a narrow vote, recommended approval of raloxifene (Evista) for the indication of breast cancer prevention in high risk women. The approval was based on data from the Study of Tamoxifen and Raloxifene (STAR) trial, which showed a reduction of 4 cases of breast cancer per 1,000 women (50% relative risk reduction), although it was not as effective as tamoxifen in preventing noninvasive breast cancers. Similar findings were seen in the Raloxifene for Use for The Heart (RUTH) trial although this trial revealed a higher risk of fatal stroke and blood clots with raloxifene. The FDA generally follows its advisory committee recommendations. Raloxifene is already approved for the prevention of osteoporosis.

The FDA has approved restricted use of tegaserod (Zelnorm) for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation in women under the age of 55 who meet certain criteria. The drug was taken off the market earlier this year when it was linked with a higher risk of cardiovascular events including heart attack, stroke, and unstable angina. Patients must have no history of heart disease and must be in critical need of the drug. Prescribing will be under an investigational new drug protocol program that has been set up by the FDA.

Rosiglitazone (Avandia-GlaxoSmithKline) is associated with an increase risk of heart failure and myocardial infarction. Despite this, the FDA's Endocrinologic and Metabolic Drugs Advisory committee along with the Drug Safety and Risk Management Advisory Committee has advised that the drug stay on the market, albeit with increased warnings. Type 2 diabetes patients who are on insulin for those with heart disease are not the candidates for the drug. The FDA will render a final decision on the drug this fall. ■