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INSIDE

ApoA-1 Milano: What's the Fuss?

ABSTRACT & COMMENTARY

THIS WIDELY PUBLICIZED SMALL TRIAL HAS CATAPULTED THE mutant form of ApoA-1 Milano into the limelight. Many investigators have been working with this interesting lipoprotein since it was discovered in the 1980s that 38 carriers from a small village in Northern Italy have very low HDL levels but very little vascular disease. The substitution of a cysteine moiety for an arginine in the lipoprotein ApoA-1 complex results in ApoA-1 Milano, which appears to have marked protective qualities with respect to the development of atherosclerosis. Esperion, a small biotech company, has produced a recombinant form of ApoA-1 Milano complexed with phospholipids.

In this study, 47 patients who presented with an acute coronary syndrome within 14 days completed the protocol, consisting of 5 weekly intravenous injections of the recombinant ApoA-1 Milano/phospholipid complex. The experimental agent was given in 2 doses, with randomization to placebo and active treatment in a 1:2:2 treatment group ratio. Five doses of placebo or the lipoprotein were given in blinded fashion over 5 weeks. All subjects had IVUS investigation of their coronary tree before treatment and within 2 weeks following the final dose. Inclusion criteria included the presence of at least a 20% narrowing in a major epicardial coronary vessel with no more than a 50% narrowing, and a minimum target atherosclerotic segment length of 30 mm; this was the segment used for analysis. Assessment of the global atheroma volume of the artery, as well as the maximal average change in the atheroma thickness and change in atheroma volume within the most and least severely diseased 10 mm long segments in the vessel, was chosen for evaluation.

Images were obtained at 30 frames per second every millimeter with a mechanical motorized pullback. Slices of 0.5 mm each were obtained over a pullback length of 30-80 mm. Analyses of the cross-sectional area inside and outside the external elastic membrane were made within the atheroma area, as well as with maximum measurable atheroma thickness. Coronary angiography was also performed and the angiographic end point was a change in mean coronary diameter at baseline and follow-up. A total of 4000 IVUS cross sections were

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analyzed at the core laboratory at the Cleveland Clinic; the mean pullback length was 49 mm, resulting in an average of 86 analyzable cross sections per patient. The primary end point was a change in percent atheroma volume at the end of the study in the combined 2 active treatment groups. Thus, a positive result would be a negative change in percent atheroma volume (decreased in atheroma). In the placebo patients, the mean change was 0.14%, with a median change of 0.03% , neither different from baseline. However, the combined treatment groups that received ApoA-1 Milano had a reduction in percent mean atheroma volume of 1.06%, with a 0.8% reduction in the median volume (P = .02). Secondary end points included mean total atheroma volume, which decreased in the active treatment cohort by 14.1 mm^3 (P = .001) vs a change of -2.9 mm^3, compared to baseline (P = NS). The maximal atheroma thickness in the active treatment group was -0.04 mm, median change -0.03 mm ($P \leq$ .001). In the placebo patients, the thickness change was -0.008, median 0.009, which was not significant. There was predominant regression of atheroma disease in the most severely diseased 10 mm segment ($P \leq .001$) but no treatment effect noted in the less severely diseased subsegments. Neither placebo nor the combined treatment subgroups had a demonstrable alteration in luminal diameter on coronary angiography. Nissen and associates conclude that "the current study provides compelling evidence of atherosclerosis regression following short-term treatment with the exogenous HDL mimetic . . . these results should be confirmed in a larger, long-term study with clinical end points." Nissen et al point out that the degree of regression was substantially greater over 5 weeks than the changes noted in prior positive angiographic trials, with a 1% decrease in atheroma volume and -4.2% in global atheroma volume in the ApoA-1 Milano cohorts. Much of the reduction in atherosclerosis burden occurred within the vessel wall internal to the external elastic membrane; furthermore, regression of disease was greatest in the most severely diseased 10 mm subsegment ($P \leq .001$).

Nissen et al stress "the rapidity and magnitude of the changes in atherosclerotic disease burden" and suggest that this is the most rapid regression of atherosclerosis yet documented. They stress that the degree of regression over 5 weeks was greater than that found in 3 years in the HATS trial with simvastatin and niacin. They believe that the mechanism of ApoA-1 Milano/phospholipid in diminishing atherosclerosis is probably due to enhanced reversed cholesterol transport, and they postulate that this compound forms a large HDL particle that "may be particularly active" in this regard, concordant with in vitro experiments. The speed of regression suggests a "more dynamic process," and Nissen et al postulate that if these results can be replicated, drugs that work to enhance reverse cholesterol transfer might be used immediately following an acute coronary syndrome for weeks to months, with conversion to oral statin later. Nissen et al emphasize that the IVUS technique, providing a 360° view of the blood vessel wall, permits "shorter duration studies in smaller numbers of patients than previously possible from interventional methods." Finally, Nissen et al make the point that their study represents a "proof of concept" approach that "must be explored in larger trials" (Nissen SE, et al. *JAMA*. 2003;290:2292-2300).

COMMENT BY JONATHAN ABRAMS, MD

This publication suggests a truly exciting approach to reversing atherosclerosis. This was the first of 2 recently reported trials that have induced an era of IVUS-mania. At the American Heart Association meeting in Orlando, Nissen also presented the results of the REVERSAL trial, which also used intravascular ultrasound, demonstrating that a high dose of atorvastatin was able to prevent progression of coronary atherosclerosis over an 18-month period, when compared to 40 mg of pravastatin, which was associated with continued progression of the disease. It is unlikely that large IVUS trials with thousands of patients would be practical; we should anticipate expansion of smaller trials because of the compressed time

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interval in which to make observations of treating atherosclerosis with a variety of pharmacology approaches, including new lipid approaches such as cholesterol ester transport protein inhibitors or enhanced ABCA-1 transporter activity. An important point to remember is that in the ApoA-1 Milano trial, angiographic evidence supporting regression was not demonstrated, thus emphasizing the remarkable sensitivity of the IVUS method, allowing for regression to be seen in just over 1 month. Whether ApoA-1 Milano will become an effective therapy is unknown at this time. There does not appear to be an oral formulation. The questions and problems stimulated by this study are elegantly discussed in an accompanying editorial by Dan Rader.[1] His comments are highly recommended to the interested reader.

It would appear that at least 2 major developments from this fascinating study are noteworthy: 1) The recombinant mutant ApoA-1 Milano induced regression of atherosclerosis with results that are concordant with many previous observations made with HDL arising from this noted Italian town where the naturally occurring variant A-1 lipoprotein was first discovered more than 20 years ago; and 2) The IVUS technique, available for many years and particularly popularized by Nissen et al at the Cleveland Clinic, appears to be a very promising technique for the rapid evaluation of lipid-modifying approaches. I believe that these results firmly underscore the reality that our view of dyslipidemia being LDL-centric needs to be modified. It is often stated that low HDL is a better independent predictor of coronary disease than high LDL. This study should encourage those investigating various aspects of reverse cholesterol transport or other approaches for attacking atherosclerosis, as mentioned above. The future looks bright. This study is but one battle, yet it signifies that perhaps the war against atherosclerosis can ultimately be won. ■

Reference

1. Rader DJ. *JAMA*. 2003;290:2322-2324.

Catheter Ablation for Paroxysmal Atrial Fibrillation

ABSTRACT & COMMENTARY

Synopsis: *In patients without structural heart disease and normal left atrial size, left atrial ablation provides a higher success rate than segmental pulmonary vein ostial ablation.*

Source: Oral H, et al. *Circulation*. 2003;108:2355-2360.

In this paper, oral and colleagues compared 2 current ablation techniques in patients with paroxysmal atrial fibrillation. Eighty patients with paroxysmal atrial fibrillation were randomized to undergo pulmonary vein isolation either by segmental ostial ablation or by left atrial ablation. The segmental ostial ablation technique requires 2 transseptal catheters. A multipole lasso catheter is placed in the ostia of each of the pulmonary veins. Circumferential lesions are then placed with a second catheter to electrically isolate each vein. This is assessed during the case by looking for the disappearance of pulmonary vein potentials during atrial pacing. The left atrial ablation technique used an 8 mm tipped catheter to construct an electroanatomic map of the left atrium. Circular lesions were placed around the left and right pulmonary veins using the electroanatomic data for catheter positioning. The circumferential lines were connected with an ablation line along the posterior left atrium. Finally, ablation was performed along the mitral isthmus between the inferior portion of the left-sided encircling lesion and the lateral mitral annulus. After the ablation procedure, patients were followed for recurrent paroxysmal atrial fibrillation. Occurrences during the first 2-4 weeks were not included in the analysis.

There were 40 patients in each group. The mean age was 51 ± 10 for the segmental ablation group and 54 ± 11 for the left atrial ablation group. Both groups had 31 men and 9 women. Only 3 patients in the segmental ablation group and 1 patient in the left atrial ablation group had structural heart disease.

All pulmonary veins in each of the patients in the segmental ablation group were successfully isolated. The total duration of radiofrequency applications needed to isolate the veins was 18 ± 9 minutes per patient. The total duration of the procedure was 156 ± 45 minutes. In the left atrial ablation group, the mean total duration of radiofrequency energy applications was 42 ± 14 minutes with a total procedure time of 149 ± 33 minutes. Although the duration of energy application was longer in the atrial ablation group, the total procedure time was not increased since electrical measurements were not required. The mean total fluoroscopy times were 50 ± 17 minutes for segmental ostial ablation compared with 39 ± 12 minutes for left atrial ablation ($P = .06$).

After the first ablation procedure, atrial fibrillation recurred in 13 of 40 patients (32%) who underwent segmental ostial ablation and in 4 of the 40 (8%) patients who underwent left atrial ablation. Life-table analysis showed that at 6 months of follow-up, 67% of patients who underwent segmental ostial ablation were free of recurrent paroxysmal atrial fibrillation compared with 88% of patients who underwent left atrial ablation. ($P = .02$).

A repeat ablation procedure was performed in 7 patients in the segmental ostial ablation group. Recovery of con-

duction in one or more pulmonary veins was seen in all of these patients. Repeat isolation was carried out, and these patients subsequently remained free of recurrent atrial fibrillation. One patient in the left atrial ablation group developed left atrial flutter and required a repeat procedure.

Oral et al conclude that in patients without structural heart disease and normal left atrial size, left atrial ablation provides a higher success rate than segmental left atrial ablation.

COMMENT BY JOHN DiMARCO, MD, PhD

Techniques for catheter ablation in patients with paroxysmal atrial fibrillation are still rapidly changing. The initial proposal by Haissaguerre and colleagues[1] recommended identification of triggers for atrial fibrillation in one or more pulmonary veins or other atrial sites and isolation of only the veins or sites that produced triggers. It was soon found that triggers were difficult and tedious to reproduce at the time of study, and most centers now try to isolate all pulmonary veins in the majority of patients. Assessing electrical isolation is technically difficult during an ablation since 2 catheters in the left atrium are required. To overcome these problems, Pappone and colleagues[2] have proposed an anatomically based approach, which draws large circles around the pulmonary veins using electroanatomical mapping. Electrophysiologic testing during the procedure is not routinely performed. Placement of the lesions is guided by the electroanatomic mapping, not by electrophysiologic findings. The proposed advantages of the latter technique are that it requires only a single transseptal catheter and that it places lesions far from the orifice of the pulmonary veins, therefore minimizing the risk for late pulmonary vein stenosis.

This paper by Oral et al shows that in a large, experienced center, left atrial ablation, as a single procedure, seems to be more effective than segmental pulmonary vein ostial ablation.

It should be noted, however, that the patients in this study were relatively young and for the most part had either normal left atrial size or only mild left atrial enlargement. The real challenge in patients with atrial fibrillation is whether the current ablation techniques can be extended to patients with a history of structural heart disease and/or left atrial enlargement. These patients form, by far, the largest group of patients with atrial fibrillation, and they are the ones in whom ablation has been the least successful. ■

References

1. Haissaguerre M, et al. *N Engl J Med*. 1998;339: 659-666.
2. Pappone C, et al. *J Am Coll Cardiol*. 2003;42:185-197.

Prophylactic Catheter Ablation in Asymptomatic WPW Patients

ABSTRACT & COMMENTARY

Synopsis: *Young patients with inducible AV reentrant tachycardia or multiple accessory pathways should undergo ablation, if possible.*

Source: Pappone C, et al. *N Engl J Med*. 2003;349: 1803-1811.

THE OPTIMAL MANAGEMENT OF ASYMPTOMATIC individuals in whom preexcitation is noted on an electrocardiogram has long been controversial. Although atrioventricular (AV) reentrant tachycardia is the most common presenting arrhythmia in patients' manifest preexcitation, occasional patients may present with rapidly conducting atrial fibrillation or even ventricular fibrillation and cardiac arrest. Catheter ablation in patients with preexcitation is both very effective and is associated with a low risk of complications in experienced hands. Despite this, however, current guidelines do not recommend invasive evaluation of most asymptomatic individuals.

In this paper from 2 Italian centers, Pappone and colleagues report the results of a randomized trial of prophylactic catheter ablation in previously asymptomatic patients with Wolff-Parkinson-White syndrome (WPW). Pappone et al had previously reported results of a prospective follow-up after a diagnostic electrophysiologic study in patients who did not undergo catheter ablation.[1] In that prior study, they had shown that the ability to induce AV reentrant tachycardia or sustained atrial fibrillation, younger age, and the presence of multiple accessory pathways were risk factors for future arrhythmic events.

In the current study, they randomized patients with high-risk characteristics at their baseline study to either ablation or routine follow-up. Based on their previous experience, patients were considered high risk if they were younger than 35 and had inducible AV reentrant tachycardia or atrial fibrillation. Ablation was performed using standard techniques. Follow-up was maintained after the procedure with periodic ECG monitoring and clinic visits.

Among the 224 patients who underwent a baseline study, 148 were classified as being at low risk, and 76 were classified as being at high risk. Four high-risk patients withdrew consent and were excluded from the study. As a result, there were 37 high-risk patients in the ablation group and 35 in the control group. In both groups, the age range was 15-30 with an equal distribu-

tion of men and women. Most patients had relatively short refractory periods of their accessory pathways. The median anterograde refractory period was 240 msec in both groups at baseline and 200 msec after isoproterenol. About one-third of the patients in both groups had multiple accessory pathways, an unusually high proportion. AV reentrant tachycardia was the most commonly inducible arrhythmia (63% in both groups). In about one-half of these patients, the AV reentrant tachycardia was observed to degenerate into atrial fibrillation. Nonsustained atrial fibrillation was the inducible arrhythmia in 37% of the patients.

Catheter ablation was successful in all 37 patients in the ablation group. Two of these patients had arrhythmic events during a median follow-up of 27 months. In both patients, the arrhythmic events were AV nodal reentrant tachycardia. Both of these patients successfully underwent a second ablation procedure for modification of the slow AV nodal pathway and have remained arrhythmia-free.

The 35 control patients were followed for a median of 21 months. All patients continued to manifest ventricular preexcitation on their electrocardiograms. Twenty-one of the 35 patients (60%) had an arrhythmic event during follow-up. The arrhythmic event was supraventricular tachycardia in 15 patients, atrial fibrillation in 5 patients, and cardiac arrest with resuscitation from ventricular fibrillation in 1 patient. The latter patient had multiple septal accessory pathways documented at his original study.

Among the 148 asymptomatic patients who were thought to be at low risk, only 6 (4%) developed arrhythmic events during follow-up, and none died suddenly.

In the control group, all patients who had inducible AV reentrant tachycardia later developed arrhythmic events. Among the patients who had only inducible nonsustained atrial fibrillation, 53% remained asymptomatic during the 5-year follow-up.

Pappone et al recommend expanding recommendations for invasive evaluations of asymptomatic patients with WPW. They recommend that patients without inducible AV reentrant tachycardia or sustained atrial fibrillation at baseline and patients older than 35 should not undergo prophylactic ablation. Young patients with inducible AV reentrant tachycardia should have their accessory pathways ablated. However, patients with only inducible nonsustained atrial fibrillation may be followed since arrhythmic events are less common. Finally, this paper confirms that patients who have multiple accessory pathways are at particularly high risk and should undergo ablation if possible.

COMMENT BY JOHN DiMARCO, MD, PhD

This paper confirms the safety and efficacy of catheter ablation in patients with WPW. Pappone et al selected a relatively young group of patients whom they characterized as "high risk" based on their prior experience. Given the known effectiveness of catheter ablation in patients with accessory pathways, it is not surprising that there was a difference in arrhythmic events during follow-up between the ablation group and the control group. There are, however, several factors in addition to those mentioned here that should also be considered when deciding whether to proceed with an electrophysiologic study and possible catheter ablation in an asymptomatic patient.

The surface electrocardiogram can often be used to localize an accessory pathway. Anteroseptal, epicardial, and midseptal accessory pathways may be technically challenging to ablate. With anteroseptal pathways, there is an increased risk of producing AV block since the accessory pathway is located close to the normal conduction system. In a truly asymptomatic patient, I would hesitate to attempt an ablation in this situation even if AV reentry could be induced. The recent introduction of cryo-thermal ablation techniques, which allow monitoring of conduction during the lesion before permanent damage is inflicted, however, may make even these patients candidates for ablation. Patients with epicardial or midseptal pathways also present problems. In these patients, standard techniques for ablation on the AV ring may not be successful and higher-risk procedures with ablations either via a pericardial approach or an approach through the coronary venous system may be required. In these patients also, I would not recommend ablation until symptoms had developed.

In the past, noninvasive techniques were used to assess future risk for sudden death in patients with WPW. These techniques were usually based on the disappearance of preexcitation on the surface electrocardiogram either at normal rates or with exercise. Although this may be a predictor of a short anterograde effective refractory period, there is not a good correlation between antegrade and retrograde refractory periods, and this technique is not effective for assessing risk for AV reentrant tachycardia. However, most patients will survive an episode of AV reentry and, if they have intermittent preexcitation, rapid rates during atrial fibrillation are uncommon.

Based on the data in this paper and the previous paper from this group, it now seems that individuals younger than 35, or perhaps 40, in whom a delta wave is found consistently on routine electrocardiograms should be offered electrophysiologic study. If AV reentrant tachycardia is induced and the pathway is not in a high-risk location, then ablation should be performed. ■

Reference

1. Pappone C, et al. *J Am Coll Cardiol*. 2003;41:239-244.

Normal Thickness Pericardial Constriction

ABSTRACT & COMMENTARY

Synopsis: *Pericardial thickness was not increased in 1 out of 5 patients with clinical evidence of constrictive pericarditis who underwent pericardiectomy and improved postoperatively. Thus, pericardiectomy should not be withheld in patients with clinical evidence of constrictive pericarditis and normal pericardial thickness.*

Source: Talreja DR, et al. *Circulation*. 2003;108:1852-1857.

SINCE THE HEMODYNAMIC CHARACTERISTICS OF constrictive pericarditis and restrictive myocardial disease are often similar, a determination of normal pericardial thickness is thought to rule out constrictive pericarditis. However, reports of pericardial constriction with normal pericardial thickness exist. Thus, Talreja and colleagues from the Mayo Clinic in Rochester, Minn, reviewed biopsy specimens and clinical features of 143 patients who had pericardiectomy for proven pericardial constriction. The patients were divided into 2 groups: 26 (18%) with pericardial thickness < 2 mm (nlThick) and 117 with > 2 mm (Thick). Previous cardiac surgery was the most common cause in nlTh (42%), and idiopathic was most common in Thick (31%). Age, comorbidity, clinical features, x-ray visualization of pericardial calcium, or hemodynamics were not markedly different between the 2 groups. Postsurgical improvement in hemodynamics was similar in the 2 groups. No patient in nlTh had a normal pericardium on histology; most had focal fibrosis or calcium. Mortality was not different perioperatively or late. Talreja et al concluded that pericardial thickness was not increased in 1 out of 5 patients with clinical evidence of constrictive pericarditis who underwent pericardiectomy and improved postoperatively. Thus, pericardiectomy should not be withheld in patients with clinical evidence of constrictive pericarditis and normal pericardial thickness.

COMMENT BY MICHAEL H. CRAWFORD, MD

The decision to refer someone for thoracic surgery to strip the pericardium is always difficult, given the clinical uncertainty of the diagnosis of constrictive pericarditis. I used to rely on imaging evidence of pericardial thickening to reassure myself that I was making the right decision. In this series, 72% of the patients had a thick pericardium by CT—11% of the normal thickness group and 86% of the thick pericardium group. Would MRI have done a better job? Regardless, this report clearly makes requiring imaging evidence of pericardial thickening untenable, so how do we arrive at a comfort level with the decision to operate? No clinical, echocardiographic, or hemodynamic parameter emerged as a highly accurate measure. The best were 2 hemodynamic measures: diastolic pressure equalization present in 77% and the classic dip and plateau of the right ventricular pressure tracing in diastole, also present in 77%. Interestingly, atrial enlargement was found in 61% of their patients, which is one of the classic features of restrictive cardiomyopathy. Talreja et al used myocardial biopsy when they were uncertain, which they were in 7 patients, all of whom showed no evidence of restrictive cardiomyopathy on histology.

There are problems with this study, which temper Talreja et al's conclusions. It is a retrospective study of only patients with a very strong suspicion of constrictive pericarditis who underwent surgery. There is no control group. Are there patients with thick pericardiums who do not have constriction? What about the patients in whom the diagnosis of constrictive pericarditis was seriously considered but rejected. What happened to them? Also, this is a study done at a quaternary referral center. Would the incidence of normal pericardial thickness in patients with strong clinical evidence of pericardial restriction in a less selected population be almost 20%? Also, the type of echocardiography performed was not mentioned in the study. I have been impressed that transesophageal echo is very useful for establishing the diagnosis of constriction. The bottom line on this study is that imaging evidence of normal pericardial thickness should not be used as sole criteria for withholding surgery in suspected pericardial constriction. Again, we are left with a difficult clinical decision requiring considerable judgment and bereft of one pivotal diagnostic test. ■

Acute Anterior Myocardial Infarction with Inferior ST Elevation

ABSTRACT & COMMENTARY

Synopsis: *Infarct size and LV function in patients with acute anterior MI are related to ST segment changes in the inferior leads. Those with inferior ST elevation have smaller infarcts with preserved LV function either due to a proximal RCA lesion or a mid to distal LAD lesion.*

Source: Sadanandan S, et al. *Am Heart J*. 2003;146: 653-661.

IN PATIENTS WITH ACUTE ANTERIOR MYOCARDIAL infarction (MI) the significance of inferior ECG ST-seg-

ment elevation is unclear. Thus, investigators from the GUSTO-I angiographic and the GUSTO-IIb angioplasty substudies evaluated the 1046 patients with anterior ST elevation and divided them into 3 groups: 1) those with inferior ST elevation also (n = 179); 2) those with no inferior ST changes (n = 447); and 3) those with inferior ST-depression (n = 420). Group 1 had more total ST elevation but the lowest peak CK level (1370 vs 1670 vs 2381; $P = .0001$) and the highest left ventricular ejection fraction (53% vs 48% vs 45%). Angiographically in group 1 patients, the infarct-related artery was either the left anterior descending (36%) or the right coronary artery (59%), whereas in groups 2 and 3 almost all patients had LAD culprit lesions (97%). In the RCA subgroup of group 1, the culprit lesion was usually proximal (67%); in the LAD subgroup, it was mid or distal. If ST elevation in V_1 was > V_3 it favored an RCA lesion in group 1. Sadanandan and associates concluded that infarct size and LV function in patients with acute anterior MI is related to ST segment changes in the inferior leads. Those with inferior ST elevation have smaller infarcts with preserved LV function either due to a proximal RCA lesion or a mid to distal LAD lesion.

COMMENT BY MICHAEL H. CRAWFORD, MD

Acute anterior MI with inferior ST elevation suggests the possibility of a large MI involving a dominant wrap around the apex LAD or combined occlusion of the LAD and RCA. In this study it was most likely due to a proximal RCA lesion (59%) or a mid to distal LAD lesion (36%) with limited infarct size. It is obvious in the case of a mid to distal LAD culprit lesion why infarct size would be limited, but why with a proximal RCA lesion? Sadanandan et al speculate that it is because there is a predominant right ventricular infarct and less LV damage, but they do not have ECG or imaging data to substantiate predominant RV involvement. In this study very few patients had multivessel disease, so the possibility of dual artery occlusion (not necessarily simultaneously) is unlikely but could be more common in less carefully selected patients. It is interesting that those with an isolated anterior MI (no ST changes inferiorly) had a larger MI and that those with inferior ST depression had the largest MIs. Presumably, the latter finding is due to the well-known phenomenon that the larger a single-vessel MI is, the more likely reciprocal changes will develop (ST depression). In some cases, the associated ST depression may represent ischemia at a distance due to sudden withdrawal of collateral flow to the adjacent territory of a previously occluded or severely stenosed artery. Finally, no differences in clinical event rates were observed despite the differences in MI size and LV function. This could be the result of a small sample size in this substudy of the GUSTO trials. ■

Inheritance of Sudden Arrhythmic Death Syndrome

ABSTRACT & COMMENTARY

Synopsis: *Families of SADS victims should be referred for assessment at centers with experience in inherited cardiac diseases.*

Source: Behr E, et al. *Lancet*. 2003;362:1457-1459.

A UNITED KINGDOM SURVEY OF SUDDEN ARRHYTHMIC death syndrome (SADS) in 32 victims aged 4-64 with normal hearts at autopsy and a negative toxicologic screening test evaluated first-degree relatives of these victims. Death in the victims occurred during inactivity or sleep in most (72%) but in 28% occurred during exercise. A total of 109 first-degree relatives were assessed. Familial cardiac disease was diagnosed in 7 of the 32 families (22%), and long QT syndrome was the most common suspected cause (4 of 7 families). Also, these families had a higher incidence of sudden unexplained death in other family members as compared to those without evidence of an inherited cardiac disease. Behr and colleagues concluded that families of SADS victims should be referred for assessment at centers with experience in inherited cardiac diseases.

COMMENT BY MICHAEL H. CRAWFORD, MD

The conclusions of this study are supported by data and common sense. Unfortunately, we have no information as to whether the identification of an inherited cause of SADS by family evaluations actually saves lives or just creates a lot of cardiac cripples. Also, genetic testing is not universally embraced. In fact, only 74% of the first-degree relatives agreed to be evaluated, and few had sophisticated testing beyond an ECG and an echocardiogram. Consequently, other conditions such as Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia and more subtle long QT cases were probably underdetected. What genetic testing that was done was disappointing since in only 2 of the 7 families were known disease-causing mutations found. However, even in well-documented clinical cases, genetic testing is not always fruitful in long QT syndrome (successful in two-thirds) and Brugada syndrome (successful in 10-20%). Finally, this type of research is difficult to do because grief-stricken families are not always agreeable, nor are institutional research boards supportive. Thus, Behr et al are to be congratulated for deriving any meaningful data from this small cohort. Although not ideal,

this study clearly shows that inherited disease can be discovered in about 1 of 5 families of SADS victims. Whether such efforts will be rewarded by future lives saved is currently unclear, but I believe most families would want such information, and efforts to inform and evaluate them seem reasonable. ■

Beta-Blockers and Dipyridamole Sestamibi Studies

ABSTRACT & COMMENTARY

Synopsis: *Beta-blocker pretreatment may underestimate the presence and severity of CAD by dipyridamole sestamibi SPECT.*

Source: Taillefer R, et al. *J Am Coll Cardiol*. 2003; 42:1475-1483.

ALTHOUGH BETA-BLOCKERS ARE KNOWN TO REDUCE the sensitivity of exercise and dobutamine sestamibi SPECT imaging for the detection of coronary artery disease, little is known about their effects on vasodilator stress scintigraphy. Thus, Taillefer and colleagues studied 21 patients with catheter proven coronary artery disease during 3 different treatments on different days assigned in a random fashion: placebo, IV administration of low-dose metoprolol, and high-dose metoprolol. The high-dose metoprolol was predetermined in each patient by titration to predefined end points. Low dose was 50% of the high dose. After each pretreatment, dipyridamole SPECT was performed and interpreted by blinded experienced observers. The resting comparison study for the stress studies was done on a different day. The sensitivity of SPECT was 86% on placebo vs 71% with low- and high-dose metoprolol. Also, the summed stress score, a measure of ischemic severity, was significantly lower on metoprolol (12 vs 8.7 vs 9.3; $P < .001$). Metoprolol lowered the pretreatment heart rate and blood pressure product (RPP). Dipyridamole increased heart rate and decreased blood pressure in each treatment setting, but RPP at peak stress was significantly lower on low- or high-dose metoprolol (10,470 vs 9440 vs 9480; $P < .01$). Taillefer et al concluded that beta-blocker pretreatment may underestimate the presence and severity of CAD by dipyridamole sestamibi SPECT.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

Beta-blockers have been proven in double-blind, placebo-controlled studies to reduce objective evidence of exercise-induced ischemia, and they are highly effective therapy for angina pectoris. Therefore, it is not surprising that they have been shown to reduce the sensitivity of exercise and dobutamine stress tests for the detection of CAD. Since dipyridamole usually does not induce frank myocardial ischemia, many believe it is impervious to beta-blockade. This study clearly shows otherwise, although the reasons are not clear. There are several caveats, however. This was acute beta-blockade in patients off antianginal drugs for 24-48 hours. Whether chronic beta-blockade would be similar is likely but not certain. Also, the effects of adenosine vs dipyridamole are not known but would probably be similar. In addition, this was a small group of highly selected patients who could safely be off antianginal drugs and undergo 3 stress tests over several weeks. The data suggest that beta-blockers should be withheld prior to all stress testing for the purpose of detecting CAD, if possible. ■

CME Questions

1. **An infusion of ApoA-Milano produced marked changes in coronary atheroma volume as detected by:**
   a. coronary angiography.
   b. IVUS.
   c. MRA.
   d. electron beam CT.

2. **Selection criteria for prophylactic catheter ablation in asymptomatic WPW patients include:**
   a. age younger than 35 years.
   b. inducible AV reentrant tachycardia.
   c. multiple accessory pathways.
   d. All of the above

3. **In younger patients with nonvalvular atrial fibrillation, which ablation technique is most successful in preventing recurrences?**
   a. Culprit pulmonary vein
   b. All pulmonary veins
   c. Left atrial
   d. Left atrial appendage

4. **In suspected constrictive pericarditis, surgical removal of the pericardium should not be performed if:**
   a. diastolic pressures are not equal.
   b. diastolic RV dip and plateau is absent.
   c. CT shows normal pericardial thickness.
   d. None of the above

5. **A falsely negative dipyridamole sestamibi stress scintigraphic study can occur if the patient is taking:**
   a. beta-blockers.
   b. ACE inhibitors.
   c. clopidogrel.
   d. aspirin.

Answers: 1(b); 2(d); 3(c); 4(d); 5(a)

PHARMACOLOGY WATCH

Vioxx Might Control Postoperative Knee Pain

Oral rofecoxib (Vioxx) may have a role in controlling postoperative pain patients undergoing knee surgery. Researchers in Chicago enrolled 70 patients who were undergoing total knee arthroplasty and randomized them to rofecoxib 50 mg the day prior to surgery, 1-2 hours prior to surgery, and for 5 days postoperatively, then 25 mg daily for another 8 days; or matching placebo at the same times. The main outcome was postsurgical analgesic consumption and pain scores, as well as nausea and vomiting, joint range of motion, sleep disturbance, and patient satisfaction with analgesia and hematologic anticoagulation parameters. Rofecoxib resulted in significantly reduced use of epidural analgesia and in-hospital opioid consumption ($P < .05$). Pain scores were also lower in the rofecoxib group while in the hospital ($P < .001$) as well as 1 week after discharge ($P = .03$). Rofecoxib also resulted in less postoperative nausea, a decrease in sleep disturbance, as well as increased knee flexion at 1 month—including a shorter time in physical therapy to achieve effective joint range of motion. The drug had no effect on warfarin usage or INR levels postoperatively. Interestingly, Buvanendran and colleagues did not include changes in renal function or evidence of GI intolerance in the study analysis. They did conclude however that rofecoxib is effective at reducing postoperative pain and opioid consumption after major orthopedic surgery (*JAMA*. 2003;290:2411-2418).

Echinacea Has No Value for URIs

Just in time for winter, another study showed that *Echinacea* has no value for reducing the duration or severity of upper respiratory tract infections (URIs). The herbal remedy is commonly used worldwide for this indication. In this study of children in the Pacific Northwest, 707 URIs occurred in 407 children over 2 years. Three hundred thirty-seven URIs were randomized to treatment with *Echinacea* while 370 were assigned to placebo. *Echinacea* was begun at the onset of symptoms and continued throughout the infection for maximum of 10 days. Data analysis showed there was no difference in the duration of URIs with *Echinacea* or placebo ($P = .89$), and there was no difference in the overall estimate of severity of URI symptoms ($P = .69$). There was also no statistically significant difference between the 2 groups for peak severity of symptoms, number of days of peak symptoms, number of days of fever, or parental global assessment of severity of URI. Rash occurred during 7.1% of URIs treated with *Echinacea* and 2.7% of those tree with placebo ($P = .008$). The study concludes that *Echinacea* was not effective in treating URI symptoms in patients 2 to 11 years old but was associated with an increase in skin rash (*JAMA*. 2003;290:2824-2830).

Valsartan, Captopril Have Similar Benefits

Valsartan and captopril have similar benefits in patients with myocardial infarction complicated

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by left ventricular systolic dysfunction, heart failure, or both, according to a new study. Previous studies have shown that ACE inhibitors reduce mortality and cardiovascular morbidity in this group, but it was unclear if angiotensin receptor blockers (ARBs) conveyed the same benefit. In this international study, nearly 15,000 patients with myocardial infarction were randomized to valsartan, captopril, or a combination of valsartan and captopril. The primary end point was death from any cause. The median follow-up was just more than 2 years. During that time, the death rate in all 3 groups was remarkably similar (979 of 4909 deaths valsartan, 958 of 4909 deaths captopril, 941 of 4885 deaths combination [hazard ratio valsartan vs captopril 1.0; 97.5% CI, 0.9-1.11; $P = 0.98$], [hazard ratio valsartan and captopril vs captopril, 0.98; 97.5% CI, 0.89-1.09; $P = 0.73$]). The valsartan plus captopril group had the most drug-related adverse events, while in the monotherapy groups valsartan was associated with more hypotension and renal dysfunction, while cough, rash, and taste disturbance were more common with captopril. Pfeffer and associates conclude that valsartan is as effective as captopril in patients with myocardial infarction who are at high risk for cardiovascular events, but combining valsartan with captopril did not offer an advantage (*N Engl J Med*. 2003;349:1893-1906).

In-patients Likely to Continue Lipid Use

In-patients who are started on lipid-lowering therapy following coronary intervention are 3 times more likely to continue on the drugs compared to patients who are started on the same therapy as outpatients. Using data from the EPILOG trial in which patients underwent percutaneous coronary intervention for stable or recently unstable coronary artery disease, 175 patients were discharged from the hospital on lipid-lowering therapy and 1951 were discharged on no lipid-lowering therapy, with the intent to start them on treatment as outpatients. After 6 months of follow-up, 77% of patients who were started in the hospital were still taking lipid-lowering therapy compared with only 25% of those who were discharged without lipid-lowering therapy ($P < .001$). Aronow and colleagues suggest that initiation of lipid-lowering therapy in the hospital is effective strategy to enhance subsequent use of the drugs in these high-risk patients (*Arch Intern Med*. 2003;163:2576-2582).

More on Metformin/Lactic Acidosis

When it comes to the relationship between metformin and lactic acidosis, the emperor may have no cloths. The drug, which has been used to treat type 2 diabetes for more than 40 years, has always carried with it the stigma that it may cause lactic acidosis in at-risk patients. Metformin hydrochloride is a biguanide that is similar in structure to phenformin hydrochloride, which was withdrawn from the market because of a documented risk of lactic acidosis. Metformin increases glucose oxidation without substantially affecting fasting lactate production and peripheral tissues unlike phenformin, and the true rate of metformin-associated lactic acidosis has never been demonstrated. Recently, researchers from Stanford performed a thorough review of the literature on this topic and performed a meta-analysis on 194 studies involving nearly 37,000 patient years in the metformin group and 30,000 patient years in the nonmetformin group. No cases of fatal or nonfatal lactic acidosis were found in either group. Their conclusion is that there is no evidence that metformin therapy is associated with an increased risk of lactic acidosis or with increased lactate levels compared with other antihyperglycemic treatments (*Arch Intern Med*. 2003;163:2594-2602). The study is important because metformin is an effective treatment for type 2 diabetes, and has some unique properties including stabilizing weight gain or even facilitating weight loss. The drug has also recently become multisource (generic) and is affordable for diabetic patients who must pay for their medications.

FDA Notes

The FDA has approved tadalafil (Cialis), Eli Lilly and Icos Corp's entry into the lucrative phosphodiesterase inhibitor market. With the success of sildenafil (Viagra), and newcomer vardenafil (Levitra) already generating huge profits, Cialis is being touted as a longer acting, less expensive alternative for the treatment of erectile dysfunction. The drug, which exerts its effect over 36 hours, has already been dubbed "the weekend drug" in Europe, where it as been available for some time.

Bristol-Myers has received approval to market the first chewable oral contraceptive for women. The product is a new formulation of Ovcon 35 (norethindrone and ethinyl estradiol), which is spearmint flavored and can be chewed or swallowed whole. If chewed than swallowed, the woman should drink a full 8 oz of liquid immediately afterward to make sure the entire dose reaches the stomach. ■