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INSIDE

More Favorable Statin Data

ABSTRACT & COMMENTARY

The lipid-lowering arm of the anglo-scandinavian Cardiac Outcomes Trial (ASCOT) was initially reported at the American College of Cardiology meeting in Chicago in March and subsequently in *Lancet*. The study is somewhat similar to the recently reported ALLHAT trial, in that both were very large trials that enrolled individuals with hypertension randomized to 2 antihypertensive therapy arms, with a large subset of individuals treated with a statin or placebo. The ALLHAT lipid strategy failed to show a significant difference between pravastatin and placebo. In ASCOT, atorvastatin was used; this is the first large, randomized, controlled trial involving this statin to be reported.

ASCOT enrolled 19,342 patients, aged 40-79, with hypertension as well as 3 additional cardiovascular risk factors. The subjects were recruited from family practice physicians in Scandinavia, the United Kingdom, and Ireland. Eligibility was an untreated blood pressure of > 160/100 mm Hg or treated hypertension with a blood pressure of > 140/90 mm Hg. Either an elevated systolic or diastolic blood pressure meeting criteria allowed eligibility. Three additional risk factors were required: left ventricular hypertrophy, diabetes, peripheral vascular disease, prior stroke or TIA, male gender, age 55 or older, proteinuria, smoking, premature CAD, or a total cholesterol/HDL ratio of > 6. Patients were recruited between 1998 and 2000. The blood pressure arm (BP) of ASCOT is ongoing. The lipid substudy consisted of 10,305 individuals randomized to atorvastatin 10 mg daily or placebo. This population was 95% Caucasian, 81% male, with a mean age of 63. Additional risk factors averaged 3.7. The study was designed to last 5 years but was stopped by the Data Safety Monitoring Board in September 2002, because the lipid arm achieved "a highly significant reduction in the primary end point," and risk reduction was 36% (P = .0005). The average follow-up was 3.3 years. The primary end point (the same used in all major statin trials) was fatal CAD and nonfatal myocardial infarction. Secondary end points that were positive included total cardiovascular events and procedures and total coronary events. However, all-cause mortality was not lowered by atorvastatin. Of interest, fatal and nonfatal stroke were reduced by atorvastatin. Baseline lipid levels in these high-risk individuals were a total cholesterol (TC) of 209 mg/dL, and an LDL

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cholesterol of 131. At the end of the follow-up, TC had fallen to 160 and LDL-C was lowered to a mean of 87 mg/dL. There were no safety problems; cancer and abnormal liver enzymes were not different between placebo and atorvastatin. A subgroup analysis indicated that the hazard ratios were identical for all strata of baseline lipids. There was 27% reduction in all stroke (P = .02). Of interest, there was no benefit of atorvastatin in women (19% of cohort) although there were only 36 total end points in this group. ASCOT achieved much better maintenance of randomized lipid-lowering therapy compared to ALLHAT; only 15% of atorvastatin patients had dropped out at 3 years, and only 9% of placebo subjects were started on open-label statin. The drop in and drop out rates in ALLHAT were very large and are believed to have strongly contributed to the failure of that study to show a difference between pravastatin and placebo. Overall BP control in ASCOT was excellent in both groups, with a reduction of 25/14 mm Hg and an average BP of 130/80 mm Hg. The ASCOT investigators, as well as an editorial by Lindholm and Samuelsson,[1] suggest that guidelines for use of lipid-lowering agents need to be modified based on these results; they also suggest that ASCOT supports a global risk strategy to reduce cardiovascular disease rather than relying on individual lipid or BP levels. A cost effectiveness assessment is not available and hopefully will be forthcoming. Finally, in terms of absolute risk reduction, there was a decrease in absolute coronary events of only 3.4 per 1000 patient-years. The ASCOT authors agree that "there are clearly financial implications of statin use among all hypertensive patients with absolute levels of cardiovascular risk as low as those included in ASCOT" (Sever PS, et al. *Lancet*. 2003;361:1149-1158).

COMMENT BY JONATHAN ABRAMS, MD

This study is important, although not particularly surprising. This was a primary prevention cohort, predominately an older male population with a relatively modest event rate. The ASCOT placebo group experienced a 9.4% estimated 10-year coronary event rate and a 7.4% 10-year total stroke rate. When both CAD and stroke are combined, the reduction in vascular risk is considerably more robust. Nevertheless, this study population was almost as low risk as the AfCAPS/TexCAPS study that had a primary event rate for CAD events of approximately 0.6% per year. The major objective of the main ASCOT trial arm is to compare 2 hypertension regimens; data supplied in the editorial indicate that excellent blood pressure control has been achieved in both active treatment groups. Thus, the lipid-lowering effects in ASCOT are in addition to a substantial reduction in blood pressure in this relatively high-risk population. It is conceivable, and perhaps even likely, that without BP control, there may have been a greater absolute reduction in risk in atorvastatin patients. Ideally, all CAD risk factors should be aggressively managed; both ASCOT and ALLHAT have demonstrated that this type of strategy can be easily applied. As mentioned above, the failure of ALLHAT to demonstrate a reduction in cardiovascular events in the pravastatin arm has been attributed to its open-label design with the substantial placebo individuals who received open-label statin, as well as the large drop out of prava statin patients, resulting in an LDL gradient at the end of ALLHAT that was rather modest. Finally, it should be stressed that ASCOT echoes and amplifies the results of the Heart Protection Study (HPS), which demonstrated that individuals at vascular risk obtained a comparable benefit from a statin irrespective of baseline lipid levels. Thus, there was an approximately 35% risk reduction in all lipid cohorts in ASCOT, including those who started with a TC of < 190 mg/dL and (an estimated) baseline LDL-C level of < 115. The actual data are not available.

In conclusion, a strategy of using overall vascular risk to qualify for a statin, even with relatively unremarkable or even low baseline total cholesterol and LDL-C levels, is confirmed by both in HPS and ASCOT. The now rather old Texas trial is confirmative, enrolling individu-

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als with only modest elevation of LDL-C and who also had depression of HDL-C, showing CV event reductions. The problem with all 3 of these studies is the large number needed to treat. In spite of unequivocal favorable cholesterol reductions, a very large number of individuals need to receive a statin in order to prevent few cardiovascular events. Thus, cost effectiveness analyses and lipid-lowering guidelines must be modified in line with what society will accept. The ASCOT investigators and the editorialists stress that current guidelines and use of statins are widely variable around the world. Nevertheless, the concept that global risk should drive preventive measures is sound. The level of total and LDL cholesterol that may benefit with active pharmacologic therapy, as well as the target end point for lipid levels, is decreasing, particularly in those individuals who have multiple CV risk factors. ■

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Timing of Surgery for Chronic Aortic Regurgitation

ABSTRACT & COMMENTARY

Synopsis: Waiting for symptom development before recommending valve replacement surgery in young patients with severe aortic regurgitation due to rheumatic disease resulted in an overall 91% survival, free of symptoms over 10 years.

Source: Tarasoutchi F, et al. *J Am Coll Cardiol.* 2003;41:1316-1324.

In many countries and parts of the united States, the major etiology of aortic regurgitation is rheumatic fever. Such patients are often younger and, accordingly, may not suffer irreversible myocardial damage if surgery is delayed until symptoms appear, rather than operating when certain echocardiographic measurements of left ventricular size and function appear. Thus, investigators at the University of Sao Paulo Medical School in Brazil, tested the hypothesis that waiting for symptoms before valve replacement surgery in chronic severe aortic regurgitation predominantly due to rheumatic fever is feasible and results in good long-term outcomes. They identified 75 asymptomatic patients (mean age, 28 years) with severe aortic regurgitation defined by a cardiothoracic index > 50 on chest x-ray; ECG evidence of left ventricular hypertrophy; a pulse pressure > 80 mm Hg; diastolic blood pressure < 60 mm Hg; and Doppler criteria. The patients were enrolled between 1988 and 1989, and were followed for a minimum of 10 years. Digitalis and diuretics were given to 30%, but none were on vasodilator drugs. Patients were seen regularly and studied by echocardiography and rest-exercise radionuclide angiography. Symptoms developed in 37 patients, who then underwent aortic valve surgery within 6 months, 30 of whom became asymptomatic after surgery. The remaining 38 remained asymptomatic and were managed medically. Thus, at the end of 10 years, 68, or 91%, were asymptomatic. The average time to symptoms was 4.6 years. Survival was 100% in asymptomatic patients and 82% in symptomatic patients. Left ventricular size and performance measurements did not change significantly over time unless the patients underwent surgery. Then there was positive remodeling observed in 92%. Interestingly, no change in left ventricular size or performance measures were observed at the time patients became symptomatic. There were no perioperative deaths, 3 patients died waiting for surgery, and 4 patients died of prosthetic valve complications. Multivariate analysis showed that baseline age and left ventricular end-systolic dimension (LVESD) were independent predictors of the development of symptoms. In patients with an LVESD > 50 mm at entry, 76% became symptomatic after 10 years (odds ratio 5.6, sensitivity 51%, specificity 84%). Tarasoutchi and associates concluded that waiting for symptom development before recommending valve replacement surgery in young patients with severe aortic regurgitation due to rheumatic disease resulted in an overall 91% survival, free of symptoms over 10 years.

COMMENT BY MICHAEL H. CRAWFORD, MD

In 1980, Henry and colleagues[1] reported that certain echocardiographic left ventricular performance measures predicted a poor outcome after valve replacement for chronic severe aortic regurgitation. This led to the concept that if these measurement cut-off points were used as an indication for surgery in asymptomatic patients, poor surgical outcomes would be avoided. Subsequent studies by Fiorelli and associates,[2] Daniel and colleagues,[3] and others done in the 1980's, using newer surgical myocardial preservation techniques, refuted this notion and suggested that one could wait for symptoms. In the 1990's, Bonow and associates[4] reported that almost all asymptomatic patients with normal initial echocardiographic values developed symptoms before

they developed left ventricular dysfunction. Thus, the ACC/AHA guidelines of 1998 list symptom development as a class I indication and achieving certain echo parameters of left ventricular size and function as class IIa.[5] This means that physicians confronting asymptomatic patients with abnormal echo indices should individualize their recommendations based upon characteristics of the specific patient. This study supports the concept that in younger patients with rheumatic aortic valve disease, waiting for symptoms to occur was associated with a favorable outcome and is a reasonable course of action. This is welcome news to clinicians who often find it difficult to convince an asymptomatic patient to undergo major surgery with significant long-term consequences.

This study was started over a decade ago, before long-term vasodilator therapy was shown to be of some benefit in such patients. Perhaps their patients would have even done better if on these agents. On the other hand, vasodilator therapy results have been reported in < 400 patients in the literature, and not all studies have shown clearcut benefits. Also, the best agent (nifedipine, hydralazine or ACEI) is unclear, as is the best dosage of administration. The excellent results in this study raise further doubt about the efficacy of vasodilator therapy for chronic aortic regurgitation.

Another interesting point is that the use of rest-exercise radionuclear angiography to assess the left ventricular function response to exercise was of no value in this study. This approach to the evaluation of left ventricular reserve in valve disease patients was popularized by Borer and associates in 1978.[6] A subsequent study by Bonow and colleagues in 1983[7] showed that the rest-exercise response was not independent of the resting ejection fraction, which was the best predictor of outcome. Despite this study, the approach has died slowly and was still in use when this study started in 1988. The accompanying editorial by Gaasch and Schick[8] points out that all but 2 patients in the Brazilian study had normal ejection fractions. Thus, they believe these data are not applicable to patients with ejection fractions < 50%, who they believe should have surgery even if they are asymptomatic. However, they agree that it may be prudent to wait for symptoms if only left ventricular dilatation is present. ■

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Mitral Valve Repair Durability

ABSTRACT & COMMENTARY

Synopsis: The durability of mitral valve repair is not constant, and the progressive incidence of more than trivial regurgitation needs to be considered in selecting a strategy for treating chronic mitral regurgitation.

Source: Flameng W, et al. *Circulation.* 2003;107: 1609-1613.

Mitral valve repair for severe nonrheumatic regurgitation is highly successful with regard to survival and freedom from reoperation for up to 10 years, but the recurrence of significant mitral regurgitation is not known. Thus, Flameng and colleagues from Leuven, Belgium, reviewed their experience with mitral valve repair done by a surgeon in 242 consecutive patients. Two-thirds of the patients had posterior leaflet prolapse and ruptured chordae. Mean EF was 66%, and average PA pressure was 40/16 mm Hg. Three-fourths were in sinus rhythm, and 85% were class II-III. Clinical and echocardiographic follow-up were performed at 1 month and every 6 months thereafter. At 8 years postrepair, clinical outcome was excellent, survival was 91%, and freedom from reoperation was 94%. However, freedom from nontrivial mitral regurgitation (> 1 ± 4) was 94% at 1 month, 59% at 5 years, and 71% at 7 years. The recurrence rate of > 1+ regurgitation was 8% per year, and 3-4+ regurgitation was 4% per year. The surgical procedure employed could only partially explain the recurrence of regurgitation. Flameng et al concluded that the durability of mitral valve repair is not constant, and the progressive incidence of more than trivial regurgitation needs to be considered in selecting a strategy for treating chronic mitral regurgitation.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

This is the first echocardiographic study to evaluate long-term freedom from mitral regurgitation following mitral valve repair. As such, it is limited because of its retrospective design and the fact that the posthospital echocardiograms were done by the individual referring cardiologists, rather than by 1 laboratory where reader

consistently could be better controlled. This is an issue since there are no universally agreed upon or applied criteria for grading the severity of mitral regurgitation. Most labs use a semiquantitative visual approach, but some try to quantitate regurgitation using PISA and other methods. Previous data have suggested that the visual distribution between trivial, mild, and mild-to-moderate mitral regurgitation is probably unrealistic. However, moderate-to-severe can usually be distinguished from lower grades. Thus, the moderate-to-severe (3 to 4+) regurgitation evaluated in this study is probably meaningful, but the > 1+ or > trivial data are suspect.

Despite these limitations, the study makes 2 cogent points. First, the incidence of moderate-to-severe mitral regurgitation is not inconsequential at 7 years (29%), but freedom from reoperation at 8 years was 94%. Other studies have shown 10-year reoperative rates of 4-7%, and 20-year rates of 20%. These results are clearly better than those observed with tissue prosthetic valves, where reoperation rates can approach 30% at 10 years, but inferior to mechanical prosthetic valves. Given that only one-third of their patients were on anticoagulants (mainly due to atrial fibrillation), these results are excellent.

Second, the constant rate of recurrence of valve regurgitation during long-term follow-up in this study suggests that the basic valvular degeneration that caused the regurgitation in the first place continues. Advanced myxomatous changes and prolapse of both leaflets increase the rate of subsequent valve failure. Other studies have shown that surgical issues dominate the recurrence of regurgitation in the first year, but that the underlying disease determines the long-term success. This study confirmed that certain surgical issues can explain some of the cases of recurrent regurgitation. The use of an annuloplasty ring, valve resection, and transposition or the use of artificial chordae, rather than chordal shortening, decreases the incidence of recurrent regurgitation.

Flameng et al's admonition that their data should be considered when discussing treatment options with the patient is well taken. Their data increase our knowledge of the unnatural history (postsurgical) of chronic degenerative mitral valve disease but unfortunately make decisions regarding treatment more difficult. For example, the fact that one-third of their patients were on anticoagulation postoperatively, mainly for atrial fibrillation, makes one wonder about the initial decision to repair, rather than replace. The management of severe mitral regurgitation continues to be difficult. ■

Natriuretic Peptides in Aortic Stenosis

ABSTRACT & COMMENTARY

Synopsis: Since natriuretic peptide levels are elevated in symptomatic patients with moderate-severe aortic stenosis, they may be useful in the management of asymptomatic patients.

Source: Gerber IL, et al. *Circulation.* 2003;107: 1884-1890.

The development of symptoms and the need for other cardiac surgery are the only class I indications for valve replacement in aortic stenosis. However, in many patients with echocardiographic evidence of severe aortic stenosis, symptom status is unclear due to inactivity or concomitant diseases. Thus, a biological marker of early left ventricular decompensation would be of value. Plasma natriuretic peptide levels are related to disease severity in aortic stenosis, but their relationship to symptom status has not been reported. Gerber and colleagues studied 74 patients with isolated aortic stenosis (peak velocity > 2.5 m/s). Independent clinical evaluation revealed that 45 were symptomatic and 29 were asymptomatic. Aortic valve area by echocardiography was smaller in symptomatic patients (0.77 vs 0.99 cm^2; $P < .0001$). Plasma natriuretic peptides were also higher in symptomatic patients (amino-terminal brain natriuretic peptide [N-BNP] 112 vs 33 pmol/L; $P = .0002$). After adjustment for age, sex, creatinine, and other compounders, N-BNP levels remained higher in symptomatic patients by 1.74 times (95% CI; 1.12-2.69, $P = .014$). Natriuretic peptide levels were also progressively higher for each NYHA class (mean N-BNP = 13, 34, 105, and 202 pmol/L, respectively). However, symptoms such as angina or syncope did not correlate with natriuretic peptide levels within each NYHA class. Angina was highly predictive of coronary artery disease at catheterization. Natriuretic peptide levels and peak aortic velocity were more predictive of symptoms (sensitivities 73-78%) than were measures of left ventriculation size and performance (sensitivities 43-70%). Gerber et al concluded that since natriuretic peptide levels are elevated in symptomatic patients with moderate-severe aortic stenosis, they may be useful in the management of asymptomatic patients.

■ COMMENT BY MICHAEL H. CRAWFORD, MD

Physicians often feel uneasy with patients who have

severe aortic stenosis by echocardiography but deny symptoms. We know prognosis is related to valve area, and when it drops to 0.7 cm^2 or less, we fear sudden cardiac death will be the first symptom the patient has. In an effort to convince reluctant patients to consider surgery by bringing out symptoms, we consider a carefully monitored low-level exercise test. However, this is dangerous, time intensive for the physician, and may not convince the patient to have surgery. Clearly, a blood test would be simpler and perhaps more persuasive.

Natriuretic peptides are a good candidate for a blood test approach since they correlate with symptoms and prognosis, including sudden death, in patients with heart failure. In this study, natriuretic peptide levels were significantly different between class I and II patients with moderate-to-severe aortic stenosis (34 vs 105 pmol/L; $P < .001$). This suggests they may be useful for decting patients with early left ventricular dysfunction before overt or recogniziable symptoms develop. Interestingly, in this study, once NYHA class was taken into consideration, there was no realtionship between natriuretic peptide levels and symptoms of angina or syncope. This suggests that natiuretic peptide levels are related to the development of dyspnea due to left ventricular dysfunction. Interpreting natriuretic peptide levels is complicated because age and sex affect the values. Thus, it is likely that natriuretic peptides will be part of our decision-making process in aortic stenosis but not the sole criterion for surgery. ■

Value of Detecting High Atrial Rates by Pacemaker Diagnostics

ABSTRACT & COMMENTARY

Synopsis: It is possible to use pacemakers to detect symptomatic and asymptomatic nonsustained atrial high-rate episodes, and detection of these atrial high-rate episodes identifies patients at higher risk for death, stroke, and atrial fibrillation.

Source: Glotzer TV, et al. *Circulation*. 2003;107: 1614-1619.

The mode selection trial (most) was a 6-year prospective, randomized, multicenter trial that compared ventricular rate modulated pacing (VVIR) with dual chamber rate modulated pacing (DDDR) in patients with symptomatic sinus node dysfunction. Patients were eligible for the atrial diagnostics substudy of MOST if they had pacemakers capable of storing a record of atrial high-rate episodes. In these patients, atrial bipolar sensitivity was programmed to 0.5 mV, and the atrial high-rate episode diagnostic was programmed on. In patients who received only ventricular pacing, the atrial lead was used for only diagnostic purposes. The atrial detection rate was programmed to 220 bpm and only atrial high-rate episodes lasting at least 5 minutes were included in the analysis. The clinicians were blinded to the atrial diagnostics data. The number of atrial high-rate episodes were counted and entered into a model as a time-dependent covariate. Cox proportional hazards were used to examine the association between atrial high-rate episodes and the primary end point, which was a composite of death, nonfatal stroke, and atrial fibrillation.

MOST enrolled 2010 patients. The atrial diagnostic substudy enrolled 312 patients who were followed for a median of 27 months. Patients in the substudy had a higher prevalence of prior supraventricular arrhythmias (60% vs 51%) than patients not in the substudy. In the substudy, the median age was 74 years, and 55% were female. In 160 of the 312 patients at least 1 atrial high-rate episode was recorded by their pacemaker. A history of SVT, a history of atrioventricular block, antiarrhythmic drug use, and heart failure were predictors of atrial high-rate episodes. The primary trial end point of death or nonfatal stroke occurred in 33 of 160 (20.6%) of the patients with atrial high-rate episodes and in 16 of 152 (10.5%) patients without atrial high-rate episodes. However, of the 10 strokes in the ancillary study population, 8 occurred in the 160 patients with atrial high-rate episodes. The presence of any atrial high-rate episode was an independent predictor of the following: total mortality, death or nonfatal stroke, and atrial fibrillation. A limited amount of ambulatory monitoring data were available from this study. Forty-one patients in the substudy had an ambulatory monitor that did not show atrial fibrillation. These 41 also had no atrial high-rate episodes detected during the monitoring. In 1 patient, the pacemaker stored an atrial high-rate episode that was not confirmed by the ambulatory monitor recordings. In 5 patients, an atrial high-rate episode detected by the pacemaker corresponded to atrial fibrillation seen on the ambulatory recording. There was no significant effect of pacing mode on the presence or absence of atrial high-rate episodes. Of the 190 DDDR patients in the sample, 95 (50%) had atrial high-rate episodes. Of the 122 VVIR patients, 65 (53.3%) had atrial high-rate episodes.

Glotzer and colleagues conclude that it is possible to use pacemakers to detect symptomatic and asymptomatic nonsustained atrial high-rate episodes and that detection

of these atrial high-rate episodes identifies patients at higher risk for death, stroke, and atrial fibrillation.

■ COMMENT BY JOHN DiMARCO, MD, PhD

It has recently been possible to program certain cardiac pacemakers to detect atrial high-rate episodes and to store these events. It has been shown that there is a high false-positive rate if relatively slow atrial rate detection criteria are used (less than 220 bpm) or if brief durations (eg, 10-30 seconds) of high rates are required. This is probably due to oversensing of either far-field ventricular signals or of T waves by the atrial lead. It also is important to note that a conservative atrial sensitivity setting of 0.5 mV on the atrial lead was selected in this study. Increased sensitivity, sometimes required to detect true atrial fibrillation, would lead to many more false positives. The data here indicate that in patients with sinus node dysfunction, pacemakers can be used to detect episodes of atrial fibrillation that may be asymptomatic. Since much of the excess mortality in patients with sinus node dysfunction is due to stroke, this would constitute an indication for anticoagulation. It is, therefore, recommended that patients with sinus node dysfunction who are known to be at risk of atrial fibrillation have pacemakers with this capability inserted. Detection of atrial high-rate episodes during long-term follow-up would lead one to consider chronic anticoagulation for those patients who are either elderly or who had other risk factors for stroke. ■

Natural History of Hypertrophic Cardiomyopathy in a Large Community-Based Population

ABSTRACT & COMMENTARY

Synopsis: Hypertrophic cardiomyopathy in the community is a benign disease associated a relatively low incidence of cardiac death. Syncope and left ventricular outflow tract obstructions are the 2 factors associated with sudden death or functional deterioration, respectively.

Source: Kofflard MJ, et al. *J Am Coll Cardiol*. 2003;41: 987-993.

This paper gives the natural history of hypertrophic cardiomyopathy in a large population of patients followed in Rotterdam, The Netherlands. Patients in this series were either diagnosed and treated at the center or were referred from the immediate community. A small group of self-referred family members are also included. The study population included 225 patients. Each patient was followed at yearly intervals after their initial examination. One hundred and thirteen patients were entered into the study between 1970 and 1990. One hundred and twelve patients were entered into the study after 1990. Noninvasive tests were performed as appropriate during the course of the study. Cardiac catheterization was performed only in patients with refractory symptoms or in preparation for surgery.

The majority of patients were male (58%). At the time of the first visit, 63 of the patients were younger than 30 years of age, and 20 were older than 65 years of age. The mean age of diagnosis was 37 ± 17 years. There was a positive family history of hypertrophic cardiomyopathy in about half of the patients, and there were 52 patients who reported sudden death in a first-degree relative. Angina (26%), dyspnea (36%), syncope (19%), and palpitations (19%) were the most common symptoms at presentation. Most of the patients had either no or minor functional impairment. At presentation, 100 patients were NYHA functional class I, 101 patients were class II, and 24 patients were class III. At echocardiography, the mean interventricular septal thickness was 21 ± 4 mm, and only 30 patients had marked left ventricular hypertrophy defined as a wall thickness greater than or equal to 25 mm. Left ventricular outflow tract obstruction was present at rest or was on provocation in 98 patients. At the time of the initial visit, 7 patients presented with persistent atrial fibrillation. Episodes of nonsustained ventricular tachycardia on a 24-hour ambulatory ECG monitor were noted in 73 of the 149 patients who had these recordings.

During follow-up, there were 44 deaths. Twenty-seven of these deaths were cardiovascular in nature, and 20 of these deaths were sudden. There were 17 deaths due to noncardiac causes. The annual mortality, annual cardiac mortality, and annual mortality due to sudden death were 1.3%, 0.8%, and 0.6%, respectively. The 5-, 10-, and 15-year cumulative cardiac survival in the entire group was 96%, 91%, and 78%, respectively. For comparison, the 15-year survival for an age map population would be about 90%. Marked left ventricular hypertrophy was not a specific marker for sudden death. Five of the patients with marked left ventricular hypertrophy died suddenly (16%) compared with 15 of 195 (7%) patients without marked hypertrophy. There was no difference in survival for patients with or without marked left ventricular hypertrophy. Deterioration in cardiac

function was more commonly associated with left ventricular outflow tract obstruction (33% vs 7%). Left ventricular outflow tract obstruction, however, did not result in sudden death with 10% of the patients with obstruction and 8% of the patients without obstruction dying suddenly. Similarly, nonsustained ventricular tachycardia was not predictive of sudden death. Sudden cardiac death was observed in 8 of 73 patients with ventricular tachycardia (11%) and in 6 (8%) of the 76 patients without VT.

A multivariate analysis for prediction of sudden death was performed using the data in the trial. This showed that only syncope was a predictor for sudden cardiac death. Left ventricular outflow tract obstruction was an independent predictor for functional deterioration.

Kofflard and associates also reported a review of the literature on prognosis and hypertrophic cardiomyopathy. The data in the current series differ from those in reports, which were largely from referral centers. In those referral centers, patients tended to be younger, had more severe presentations or had more advanced functional impairment. The series from referral centers had a total cardiac mortality that was approximately twice that observed in this community-based series. Kofflard et al conclude that hypertrophic cardiomyopathy in the community is a benign disease associated a relatively low incidence of cardiac death. Syncope and left ventricular outflow tract obstructions are the 2 factors associated with sudden death or functional deterioration, respectively.

COMMENT BY JOHN DiMARCO, MD, PhD

Hypertrophic cardiomyopathy is one of the most difficult problems with which cardiologists deal. There are a large number of mutations that result in hypertrophic cardiomyopathy. The natural history of each of these genotypes, however, has not been fully characterized. In most cases when patients present with hypertrophic cardiomyopathy, physicians do not have enough information from the family history in order to estimate their patient's prognosis. The literature on hypertrophic cardiomyopathy often focuses on high-risk series from referral centers. As shown here, patients from referral centers may not represent the true natural history of the disease. Sudden death in hypertrophic cardiomyopathy often presents early in life. Factors associated with risk of sudden death in these young individuals have been nonsustained VT on monitoring, syncope, and significant left ventricular hypertrophy. However, older individuals tend to have a more benign course. In these patients, sudden death, when it occurs, happens in the setting of advanced heart failure and is usually preceded by functional deterioration. The latter patients are more commonly seen in a community setting.

The data from this community-based study by Kofflard et al are quite instructive. It will be helpful in guiding physicians who evaluate and care for individuals older than 30 with hypertrophic cardiomyopathy. It will remain problematic how to approach younger individuals. Clearly, if a family history of sudden death is available in these individuals, aggressive therapy should be pursued. Hopefully, in the future, a better knowledge of the genetic basis of hypertrophic cardiomyopathy and the ability to predict prognosis from knowledge of genotype will be used to guide therapy. ■

CME Questions

28. In a community-based population sudden death in hypertrophic cardiomyopathy is predicted by:
a. LV wall thickness.
b. outflow gradient.
c. syncope.
d. All of the above

29. Patients with pacemakers who have high atrial rates detected have a higher frequency of:
a. mortality.
b. stroke.
c. atrial fibrillation.
d. All of the above

30. In young patients with severe aortic regurgitation due to rheumatic fever, surgery should be considered when:
a. symptoms develop.
b. LVEDD > 60 mm.
c. LVESD > 40 mm.
d. diastolic blood pressure < 60 mm Hg.

31. In asymptomatic patients with severe aortic stenosis, surgery should be considered when:
a. symptoms develop.
b there is a need for other cardiac surgery.
c. there are elevated natriuretic peptide levels.
d. All of the above

32. In high-risk patients with multiple risk factors, statins are useful:
a. if LDL-cholesterol > 160 mg/dL.
b. if LDL-cholesterol >130 mg/dL.
c. if LDL-cholesterol >100 mg/dL.
d. regardless of cholesterol levels.

33. After mitral valve repair, the incidence of moderate-to-severe regurgitation developing is:
a. 1% per year.
b. 4% per year.
c. 8% per year.
d. 12% per year.

Answers: 28(c); 29(d); 30(a); 31(d); 32(d); 33(b)