EDITORIAL COMMENT

Medical Treatment of Aortic Stenosis

Promising, or Wishful Thinking?

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Valvular aortic stenosis (AS) is a prevalent condition and one of the most common indications for valve replacement surgery. Although AS can be congenital in etiology or a consequence of rheumatic fever, the most common form is “calcific” AS. Calcific AS is usually seen in patients over the age of 65 years, and as the population continues to grow older, the number of patients with AS is almost certain to rise. Using both noninvasive and invasive techniques, a number of studies have documented that AS is a progressive disease, although the rate of progression may vary considerably from patient to patient. At present, no medical therapy has been proved effective in patients with severe AS. The management of patients with AS has been reviewed in a recent update (1). When AS causes symptoms of heart failure, syncope, or angina, prompt surgical replacement of the stenotic aortic valve is indicated. Although asymptomatic patients with AS have a relatively good prognosis, a subgroup of patients who lack symptoms at rest will demonstrate poor exercise tolerance or other worrisome features (such as hypotension or ventricular tachycardia) when they perform careful, physician-supervised exercise testing. Such patients may also be candidates for valve replacement surgery. Successful aortic valve replacement (AVR) surgery markedly improves prognosis in asymptomatic AS patients, even those with substantial left ventricular (LV) dysfunction. Except in children with congenital AS, alternative mechanical approaches to AS (such as percutaneous balloon valvuloplasty or aortic decalcification procedures) do not lead to a good long-term outcome. Thus, many patients with AS will eventually need surgical AVR. This can be carried out in experienced centers with a reasonably low operative mortality, even in AS patients with depressed LV function.

However, operative mortality and morbidity are increased in older patients with AS, particularly those with comorbidities that are not rare in the elderly: coronary artery disease, cerebrovascular disease, impaired renal function, and chronic respiratory disorders. Accordingly, a safe and effective medical therapy that would slow the progression of AS, and that might thereby alleviate the need for AVR surgery in some patients, clearly would be very promising and of considerable clinical interest.

BACKGROUND

For many years, the progression of calcific AS was considered a “wear and tear” phenomenon—a consequence of aging coupled with increased hydrodynamic stresses on the abnormal aortic valve. The concept that “scarring begets scarring” appeared to explain the observed progressive increases in transvalvular gradient and decreases in aortic valve orifice area that are seen in AS patients who are followed longitudinally. In the past decade, however, interesting epidemiologic (2–4) and histologic (5–7) similarities between AS and atherosclerosis have been reported. These conditions are not only more prevalent with increasing age, but both disorders also demonstrate associations with gender, hyperlipidemia, hypertension, diabetes, and smoking. Histologic studies of stenotic aortic valve specimens removed at AVR or necropsy demonstrate regions of chronic inflammation reminiscent of those seen in atherosclerosis, including lipoprotein deposition, cellular infiltration of macrophages and T-lymphocytes (6), and calcium (7). There is clear evidence that progression of coronary atherosclerosis can be favorably reduced or even reversed by medical therapy (8). The intriguing similarities between atherosclerosis and calcific AS have stimulated a growing interest in the possibility that medications documented to be effective in patients with atherosclerotic coronary artery disease might be used to slow the progression of AS.

CONTRIBUTIONS OF THE CURRENT ARTICLE

In the current issue of the Journal, Bellamy et al. (9) make several important additions to our understanding of AS progression. They confirm the earlier observations of other investigators that measures of AS severity show progressive increases in transvalvular gradient and decreases in valve orifice area. Importantly, the study of Bellamy et al. (9) is an extension of the prospective, population-based Rochester Epidemiology Project, in which the majority of patients were studied not because of a change in clinical status, but rather were re-evaluated systematically during follow-up even though they remained asymptomatic. Their finding that, in general, the annualized decrease in valve orifice area (AVA) was approximately 0.1 cm² is consistent with the findings of other authors (10–12). Bellamy et al. (9) also investigated the relationship between plasma lipid values and the rate of AS progression. In patients not receiving lipid-lowering therapy during follow-up, the authors found that the rate of AS progression (based on measures of transvalvular velocity, gradient, and valve orifice area) did not demonstrate a significant relation-
ship with plasma cholesterol levels (expressed either as total cholesterol (TC) or low-density lipoprotein cholesterol [LDL-C]). Rates of change of AVA were not significantly different when patients were subdivided according to TC quartiles. Neither total nor LDL-C values differed between patients in whom the annualized rate of AS progression exceeded the median value ("fast progressors") and those with progression rates less than the median value ("slower progressors"). These observations are important because some previous studies (2,4,13) have reported a positive association between hypercholesterolemia and the rate of AS progression, whereas others (14) have not. The majority of these earlier studies were retrospective analyses, however, and potentially subject to referral bias. These shortcomings were avoided in the prospective, population-based study of Bellamy et al. (9).

In nearly 25% (38 of 156) of the patients studied by Bellamy et al. (9), treatment with a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor ("statin") agent had been prescribed by the patient's treating physician. Statin treatment was not randomized, but based on clinical indications; statin-treated patients usually had not only documented hypercholesterolemia, but also documented coronary artery disease or significant coronary risk factors. Notably, patients treated with a statin agent demonstrated a significantly lower rate of AS progression during systematic follow-up (annualized mean decrease in AVA 0.04 cm²) compared with untreated patients (annualized mean decrease 0.09 cm²). Statin usage remained a significant independent predictor of the rate of AS progression even after adjustment for age, gender, and baseline AVA. Interestingly, the magnitude of decrease in TC and LDL-C values during statin therapy did not show a significant correlation with the rate of AS progression. Similar findings were noted in the 108 patients (nearly 70% of the study population) in whom repeated evaluations were performed systematically and not because of some clinical change in the study patients.

The current findings of Bellamy et al. (9) are remarkably similar to those of the earlier retrospective study reported by Novaro et al. (15). That group of investigators also noted that statin usage was an independent predictor of the rate of AS progression (with annualized mean decreases in AVA of 0.06 cm² in statin-treated AS patients, compared with 0.11 cm² in untreated AS patients), and that the relationship between the decrease in LDL-C values and the rate of change in AVA was not significant. The retrospective study of Aronow et al. (13) also noted that compared with untreated patients, statin-treated AS patients demonstrated a slower rate of progression during follow-up.

Accordingly, the prospective population-based study of Bellamy et al. (9) confirms earlier and largely retrospective reports that: 1) AS is a progressive disorder; 2) statin therapy is associated with a significant reduction in the annualized rate of AS progression; and 3) the effect of statin therapy on the rate of AS progression cannot be explained simply by changes in plasma lipids.

**Shortcomings of the Current Study**

As with all studies, it is possible, in retrospect, to identify some shortcomings. In the study of Bellamy et al. (9), statin treatment was not assigned randomly to AS patients, but rather was (or was not) prescribed by the patient's treating physician, apparently based on accepted clinical indications. Five different statin agents were prescribed, and although the doses of each individual statin agent were variable, the mean doses generally were relatively low. In addition, patients included in this study were elderly (the mean age of study patients was >76 years and statin-treated patients were on average 73 years old at the time of study enrollment). Study patients also had relatively established AS, with an average mean gradient of 22 mm Hg and a mean AVA approximately 1.2 cm². Indeed, the criteria for inclusion (baseline mean gradient at least 10 mm Hg and AVA no more than 2 cm²) would by definition exclude patients with "aortic sclerosis," those with mild leaflet thickening but only a trivial transvalvular gradient. Hence, although intriguing, the findings of Bellamy et al. (9) do not definitively prove that statin therapy is effective in reducing the rate of AS progression.

**Areas for Future Investigation**

Observations by a number of investigators over the past decade have demonstrated convincingly that aortic valve calcification and stenosis is not just a disease of aging, and that AS does not progress purely because of increased hydrodynamic stresses on the abnormal valve leaflets. Rather, progression of AS has a fascinating histologic and biochemical basis that suggests an important role of tissue injury, inflammation, and remodeling. A better understanding of the pathobiology of this process may offer insights into appropriate therapy.

Because epidemiologic studies have indicated an association between hypercholesterolemia and calcific AS, and because histologic assessment of valve tissue from patients with AS demonstrates lipoprotein accumulation and oxidation in diseased valves, it seems logical to postulate that lipid-lowering therapy might slow the rate of AS progression. The studies of Aronow et al. (13), Novaro et al. (15), and Bellamy et al. (9) all demonstrate a significant decline in the rate of AS progression in patients treated with statin agents, albeit in a nonrandomized manner. I certainly agree with the concluding recommendation of all of these investigators: a large randomized clinical trial of HMG CoA reductase inhibitor therapy in patients with AS is warranted.

The observation that the decrease in AS progression in statin-treated patients is out of proportion to the more modest decreases in plasma cholesterol measures raises the intriguing possibility that the effect of statins on AS progression might be based on mechanisms different from
simply lowering LDL-C and TC. For years, investigators have recognized that atherosclerosis has an important inflammatory component (16). Leukocyte adherence to regions of lipid accumulation, conversion of monocytes to macrophages, and formation of foam cells leads initially to fatty streaks, and eventually to local fibrosis and remodeling. Although the progression of atherosclerosis is slowed by treatment with statin agents, statin therapy also has been shown to reduce adverse ischemic events even in patients with coronary artery disease who are not hypercholesterolemic (17).

This intriguing observation appears to have a biochemical basis. HMG-CoA reductase inhibition blocks the cholesterol synthetic pathway at the level of conversion of hydroxymethylglutaryl coenzyme A to mevalonate (18). Subsequent lipid moieties include not only cholesterol, but also intermediates such as geranylated pyrophosphate and farnesyl pyrophosphate, nonsterol isoprenoids that appear to play an important role in the control of cell growth, proliferation, and secretion. It is postulated that by blocking the cholesterol synthetic pathway and reducing production of these nonsterol isoprenoids, statin agents may alter cellular behavior. Indeed, recent studies have demonstrated that HMG-CoA reductase inhibitors reduce secretion of matrix metalloproteins by macrophages (19) and cause an improvement in endothelial function by attenuating superoxide anion formation (20). Because matrix metalloproteins lead to degradation of extracellular matrix, and because endothelial dysfunction plays an important role in atherogenesis, statin agents may exert an anti-atherogenic effect through their effects on macrophage behavior.

Whether similar processes play a role in the evolution of the histologic and functional abnormalities in AS is only speculative. Clearly, AS and atherosclerosis have not only notable similarities, but important differences (21). Nonetheless, several observations are intriguing. As in atherosclerosis, chronic inflammatory cells are also present in valve leaflets from patients with aortic sclerosis and AS (5,6).

Serum levels of C-reactive protein, a sensitive marker of systemic inflammation, are also elevated in patients with established AS (22). Pravastatin was shown recently to lower the median level of C-reactive protein in a prospective, randomized community-based double-blind trial (23). Thus, the beneficial effect of statins that have been seen in patients with AS could be due to their anti-inflammatory properties.

Because valve specimens in patients with AS demonstrate not only lipid accumulation but also other histologic abnormalities, additional therapeutic approaches may deserve consideration. In AS, activated macrophages produce osteopontin, a protein that is involved in tissue calcification (24). Even early lesions of AS show areas of microscopic mineralization in association with lipid deposition and leaflet thickening (5). In patients with more advanced disease (7), dystrophic calcification, microfractures, and ossification can be seen. It is interesting to note that statin agents have been associated with a decreased risk of fractures (25), and with reduced rates of aortic valve calcium deposition as detected using electron beam computed tomography (26). These observations raise the possibility that drugs that alter calcium metabolism and ossification might also be of therapeutic value in patients with AS.

Additional research is needed to define optimal treatment. Is one statin agent more effective than another, or is there a “class effect”? What is the optimal dosage for slowing AS progression? Are statin agents effective alone, or would their efficacy be enhanced by adjunctive therapy with other anti-inflammatory agents or drugs that alter calcium metabolism? In the spectrum of AS, from valve sclerosis to critical stenosis, when should therapy be started? Are the beneficial effects of medical therapy restricted to patients with established mild-moderate AS, or would they slow (or perhaps even prevent) progression if started in patients with aortic sclerosis before they developed hemodynamic obstruction to LV emptying? Does medical treatment of AS patients result in measurable differences in outcome, such as delayed onset of symptoms, reduced need for valve replacement surgery, or improved survival?

Even though a prospective, randomized (and presumably multicenter) clinical of statin therapy in patients with AS would appear to be well warranted, I can imagine potential problems in patient recruitment and randomization. Patients with AS frequently also manifest hypercholesterolemia, hypertension, and other risk factors for coronary artery disease, which might make it difficult to assign them randomly to treatment with a placebo rather than a statin agent.

In conclusion, the cellular and molecular bases for the development and progression of AS, and the findings of studies such as that of Bellamy et al. (9), appear to offer the promise that a safe and effective medical therapy for AS is not just wishful thinking. Notwithstanding potential practical difficulties that might be inherent in conducting a large, randomized prospective trial of medical treatment in patients with AS, this condition is too prevalent, and its consequences too important, to ignore.

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