Can statin therapy alter the natural history of bicuspid aortic valves?

PATIENTS with bicuspid aortic valve (BAV) malformations, the most common congenital cardiac abnormality, are at significantly higher lifetime risk of developing aortic stenosis, aortic regurgitation, aortic root dilatation, infective endocarditis, aortic aneurysm, and aortic dissection. Unfortunately, once these complications develop, cardiac surgical intervention is required in the vast majority of symptomatic patients. Despite a better understanding of the pathophysiology and complications of BAV malformations, there are currently no medical treatment options available to alter the natural history or halt the progression of BAV-related complications. However, a question that has probably crossed the minds of many is whether statins, by virtue of their powerful cholesterol-reducing and pleiotropic anti-inflammatory and immune modulatory effects can change the natural history of BAV disease if introduced early?

BAV is the most common congenital cardiac malformation, occurring in 1–2% of the population (7, 21). Although patients with a BAV may be asymptomatic and go undetected throughout their life, the majority of these patients will develop complications requiring surgical treatment. BAV disease is responsible for more deaths and morbidity than all other congenital heart defects combined.

BAVs arise from abnormal aortic cusp formation during valvulogenesis, resulting in the formation of one aberrant cusp that is larger than a single cusp but smaller than two normal cusps. The BAV is often accompanied by congenital abnormalities of the aorta. Thus the process underlying BAV formation involves more than just the inappropriate fusion of adjacent cusps and likely represents a genetic disease that affects the entire aortic root. Although not yet confirmed, abnormalities in components of the extracellular matrix, such as fibrillin-1, or aberrant vascular matrix remodeling may contribute to abnormal valvulogenesis and a structurally weakened aortic root (6). Abnormalities in the endothelial nitric oxide synthase (eNOS) gene may also be involved because mice with eNOS deficiency have a higher incidence of congenital BAV (10). These eNOS-deficient mice may potentially serve as an experimental in vivo BAV model. BAVs appear to be genetically inherited in an autosomal dominant fashion with reduced penetrance (4, 9). With the use of echocardiography to screen the family members of patients with a BAV, 36.7% of the screened families had more than one first-degree relative with a BAV (9), suggesting that echocardiographic screening of first-degree relatives may be valuable.

BAV malformations predispose to both valvular complications and complications involving the native aorta. Aortic stenosis by far is the most common complication of BAV. Approximately 50% of patients undergoing aortic valve replacement have a BAV, and aortic stenosis tends to present much earlier in this population, generally in the fourth and fifth decades of life (21). BAVs represents the commonest aetiology of aortic stenosis between the ages of 60 and 75 yr (21). Echocardiographic studies have demonstrated that sclerosis of the BAV begins as early as the second decade of life, with calcification becoming very prominent from the fourth decade onward (2).

Once considered a degenerative, age-related condition, calcification of the aortic valve is currently thought to resemble the process of atherogenesis. Histologically, calcified regions of aortic valves have features such as the presence of lipid, inflammatory cells, and neoangiogenesis that are associated with arterial atherosclerotic plaques (12). Furthermore, patients with dyslipidemia are at increased risk of developing BAV stenosis (3). Aortic regurgitation may occur in the presence of a BAV secondary to cusp prolapse, fibrotic changes, or dilatation of the sinotubular junction, requiring aortic valve repair or replacement. Also, endocarditis is a potentially devastating complication that tends to occur in BAV patients with regurgitant valves.

The vascular complications of BAV disease are related to progressive aortic root dilatation, aortic regurgitation, aneurysm formation, and dissection. Among young patients with normally functioning BAVs, ≥50% have echocardiographic evidence of aortic dilatation, the precursor to aortic rupture and dissection, both potentially fatal events (14). BAV patients tend to have abnormalities within the aortic media, namely, matrix disruption and smooth muscle cell loss. Matrix metalloproteinases (MMPs), endogenous enzymes that degrade matrix components, have been implicated in atherosclerotic aortic aneurysm formation (20) and appear to be elevated in the aorta of patients with BAVs (6). Currently, aortic dilatation is monitored serially by echocardiography and aortic root replacement is recommended once dilatation exceeds 4 cm (5).

Statins have emerged as a powerful and safe pharmacotherapy for both primary and secondary prevention of coronary heart disease. In addition to their well-known effects on cholesterol metabolism, statins have a plethora of anti-inflammatory, vasculoprotective, and immune modulatory effects, which have been linked to their overall benefit. Indeed, these cholesterol-independent effects are credited for the benefit of statins noticed in diverse patient groups, including rheumatoid arthritis (11) and Alzheimer’s disease (22).

With the better understanding of the pathophysiology of BAV complications, it becomes apparent that statins exhibit a pharmacological profile that may potentially alter the natural history of this disease. Statins may be able to directly modify the processes that contribute to the progression of aortic stenosis in patients with apparently normal functioning BAVs (see Fig. 1). First, statins by virtue of lowering LDL-cholesterol reduce an important risk factor for BAV disease progression. Second, statins, through their powerful anti-inflammatory actions, may limit the extent of aortic valve calcification, critical to the development of BAV stenosis. Third, statins may limit aortic dilatation by reducing the production of MMPs, which are critical to the aberrant aortic remodelling seen in BAV disease. If one assumes that patients with BAV disease have an abnormal endothelium (deficiencies in eNOS), abnormal vascular matrix turnover (increased MMPs), and abnormal metabolic responses (the metabolic syndrome), then statins could be expected to limit the deterioration of the BAV and the dilatation of the aorta by improving endothelial function,
restoring MMP balance and combating the adverse effects of the metabolic syndrome. Indeed, in clinical studies, statin therapy has been demonstrated to reduce the progression of aortic stenosis (15), decrease native aortic valve calcium accumulation (19), and delay the degeneration of bioprosthetic aortic valves (1). However, these studies were not randomized, and no attempts were made to standardize the type, dose, or duration of statin treatment, and only patients with established aortic stenosis were studied. Prospective, randomized, placebo-controlled studies assessing the effect of lipid-lowering therapy on aortic stenosis disease progression are required to definitively address this issue. Currently, there are two multicenter, randomized, placebo-controlled studies being conducted to answer this question: the Canadian Aortic Stenosis Progression Observation: Measuring Effect of Rosuvastatin Study and the European Simvastatin and Ezetimide in Aortic Stenosis Study (16). The results of these studies are greatly anticipated.

Is it feasible to test the hypothesis that early statin therapy in patients with BAV may reduce BAV-associated complications? Would a positive result of such a trial be large enough to outweigh the risks of placing young, otherwise asymptomatic patients on lifetime statin therapy? On the surface, the concept may sound trite, but understandably a trial of this nature raises numerous challenges. First, identification of asymptomatic BAV patients would require mass echocardiographic screening, something that is not routinely done. Widespread echocardiography to detect BAV in asymptomatic patients is unreasonable; however, because BAVs tend to occur in families, children of affected patients could be screened and serve as study participants. Such patients may be identified from cardiac surgical databases, although the ethics surrounding this would require careful consideration. Ideally, trial patients upon entry would have a BAV with an aortic valve area of $>1.2 \text{ cm}^2$, no calcification, an aortic root diameter measured at the sinotubular junction of $<4 \text{ cm}$, no coronary or peripheral vascular disease, and normal lipids and would not otherwise be candidates for statin therapy. What would the outcome of a study like this be? Probably a composite of aortic valve area, transvalvular gradient, and other well-established complications of BAV disease, such as the development of clinically significant aortic stenosis, aortic calcification, aortic dilatation, or aneurysm formation. For argument purposes, if you were to anticipate that statins would reduce the composite of BAV complications by 15% over 5 yr, a sample size of $\approx4,000$ would be needed to provide sufficient power (80%) to detect a significant difference between groups. Probably a more refined initial strategy would be to restrict the study to patients over the age of 45 yr with an incidental observation of BAV and evidence of asymptomatic mild aortic stenosis, randomized to statin versus placebo with a 5- to 7-yr followup. The type and dose of statin are other considerations, although we would propose the use of either simvastatin (40 mg) or atorvastatin (80 mg) in keeping with evidence from the Scandinavian Simvastatin Survival Study (17), Heart Protection Study (8), and Reversal of Atherosclerosis with Aggressive Lipid Lowering (13) trials. Although statins are well tolerated and safe, with a low frequency of adverse events, is it ethical to subject patients who are otherwise not dyslipidemic to statin pharmacotherapy? The Anglo-Scandinavian Cardiac Outcomes Trial provides a good example of a case where statin therapy was tested in patients at risk of cardiovascular events, but not deemed dyslipidemic, and reported to markedly reduce cardiovascular mortality and morbidity (18).
Clearly, it would be an attractive proposition to suggest that early intervention with a widely used and relatively safe pharmacological agent could alter the natural history of the most common congenital cardiac abnormality. We believe that the time has come for cardiac surgeons and cardiologists to evaluate this premise, initially in a small select group of patients, to test whether statin therapy will hold the same promise of disease modification in BAV as it has in the world of atherosclerosis. However, it is important to stress that there remains a lack of knowledge regarding the natural history of the disease. The notion that 1–2% of the population has a BAV may not be sensitive enough to identify the presence or absence of a BAV. The time required for a cardiography may not be sensitive enough to identify the disease. The notion that 1–2% of the population has a BAV remains a lack of knowledge regarding the natural history of the disease.

REFERENCES


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