Mitral annular calcifications and aortic valve stenosis

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This editorial refers to ‘Association of mitral annular calcification and aortic valve morphology: a substudy of the aortic stenosis progression observation measuring effects of rosvustatin (ASTRONOMER) study’† by D.S. Jassal et al., on page 1542

Idiopathic mitral annular calcification (MAC) is one of the most common cardiac abnormalities found in autopsies, occurring twice as often in females than in males. It has been reported in 6.1% of the subjects that undergo a routine echocardiogram,1 and the incidence rises sharply with age. The primary pathological event in its development is considered to be a fibrillar alteration of the collagen ultrastructure that triggers lipid deposition and calcification within the annulus. Although it was initially thought that the presence of calcification of the mitral annulus had few functional consequences in most hearts, this is not the case. Patients with MAC have been shown to be at a higher risk of conduction disturbances, cardiovascular disease, and total cardiac death. Calcified aortic valve disease is also very common. The overall prevalence is 13% and increases up to 25% in adults >65 years old. Until recently, aortic calcification was thought to be caused by a passive accumulation of calcium along the aortic valve leaflet. However, there are a growing number of studies showing similarities among vascular atherosclerosis and degenerative changes in aortic and mitral valves. For instance, there is a high degree of endothelial injury in the development of calcified aortic valve disease.2 Furthermore, histological analysis of mild aortic sclerotic valves has shown a chronic inflammatory process with macrophage and T lymphocyte migration as well as lipid accumulation. A correlation has also been demonstrated between serum high sensitivity C-reactive protein (hsCRP) levels and the severity of aortic valve stenosis.3 These experimental observations endorse epidemiological and clinical studies that have shown an association among clinical risk factors, both calcification of the mitral annulus and aortic valve and systemic calcified atherosclerosis.4 Therefore, these convincing data support the hypothesis that cardiac valve calcification is an active biological process due to atherosclerosis that could be targeted with medical therapy to prevent or slow disease progression. Aiming to confirm this hypothesis, several studies have evaluated the effects of statins and angiotensin-converting enzyme inhibitors (ACEIs) in this process. The majority have shown a significant reduction in disease progression under statin therapy.

The magnitude of these effects was assessed by measuring the annual increase in valve calcium,5 the increase of the peak gradient,6 or the decrease in valve area by Doppler echocardiography.7,8 More recently, Rosenhek et al.9 studied the effects of ACEIs, statins, and their combination on the haemodynamic progression of aortic stenosis (AS). They concluded that only statin therapy appears to reduce the progression of both mild to moderate and severe AS. However, they also observed an unexpected marked discordance between serum lipid levels and haemodynamic disease progression, which suggests that the effect of statins may be due to anti-inflammatory properties rather than lipid-lowering effects. A recent survey by Moura and colleagues10 looked prospectively at the effect of rosvustatin on the progression of moderate to severe AS. After a mean follow-up of 73 ± 24 weeks, they found that the group of patients under statin therapy showed a significant reduction in the progression of AS. Additionally, the authors described a correlation among the improvement in peak jet velocity, mean gradient, and aortic valve area with the change in low-density lipoprotein (LDL) cholesterol levels. The RAAVE study (Rosuvastatin Affecting Aortic Valve Endothelium) was the first prospective study to demonstrate the beneficial effect of statin therapy in AS. Currently, ongoing randomized trials will provide further evidence on the treatment of this complex disease.

The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study11 is a randomized, double-blind, placebo-controlled, multicentre ongoing trial investigating the effect of intensive lipid-lowering therapy on the progression of mild to moderate AS. The SEAS
study will be the largest randomized trial to evaluate whether therapy with 40 mg of simvastatin and 10 mg of ezetimibe (vs placebo) can retard the progression of aortic valve stenosis and, thereby, defer surgery, relieve adverse consequences of AS, and possibly decrease mortality and morbidity in these patients.

Although both the ASTRONOMER and SEAS studies included similar echocardiographic variables, the SEAS study enrolled a larger population of patients (n = 1873 vs n = 272) and had longer treatment duration (4–7 vs 3–5 years). Moreover, primary efficacy end-points of the SEAS study included aortic valve surgery, ischaemic vascular events, and cardiovascular mortality. Altogether, the ASTRONOMER and SEAS studies should help to determine whether intensive lipid-lowering treatment: (i) confers cardioprotective benefits in AS patients; and (ii) if such benefits exist, when this treatment should be commenced. The ongoing trials will help in assessing the uncertainties raised by prior clinical studies regarding lipid-lowering therapy in AS patients.

Jassal and colleagues\(^\text{12}\) evaluated the association of baseline MAC with aortic valve morphology in an observational study of asymptomatic patients enrolled in the ASTRONOMER trial. Transthoracic echocardiography was performed in the 219 patients, and the study population was divided into bicuspid and tricuspid aortic valves. Echo measurements included left ventricular dimensions, aortic root dimension, MAC, and aortic valve calcification. The degree of valve calcification was semi-quantitated based on severity (from absent to severe). The results convincingly demonstrated a significantly higher degree of MAC in patients with tricuspid aortic valve after adjusting for age and systolic blood pressure. The authors concluded that in patients with asymptomatic mild to moderate AS, MAC is more prevalent in those individuals with a tricuspid aortic valve, independently of age and systolic blood pressure.

As outlined above, MAC and aortic valve calcification represent a chronic, degenerative process in the fibrous skeleton of the heart that has been associated with atherosclerosis. This process may accelerate when mechanical stress is increased, as it usually occurs in hypertension and congenital or acquired valvular disorders. There are some studies that suggested an association of MAC with AS. Their main aim was clarifying if MAC and aortic valve calcification are the result of a primary degenerative process that increases with age, an expression of generalized atherosclerosis, or the outcome of increased valvular stress. With regard to the third hypothesis; Fulkerson et al.\(^\text{13}\) reported in 1979 that chronic increase of left ventricular pressures, as it predisposes to the heart, is related to the presence of cardiovascular risk factors in all our patients, and with special attention to those presenting with MAC, as this could be a marker of further cardiac disorders and atherosclerosis. Future studies will probably provide additional evidence for this hypothesis and, more importantly, will elucidate whether the degree of MAC can predict the response to statins in patients with AS.

**Conflict of interest:** none declared

**References**


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**CLINICAL VIGNETTE**

Evaluation of a fibroelastoma with magnetic resonance imaging

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A 64-year-old woman was admitted to hospital with acute chest pain and self-limiting ventricular tachycardia. Transthoracical Doppler echocardiography demonstrated mitral regurgitation and a mobile mass close to the anterior leaflet. Coronary angiography was normal. For clinical evaluation preoperatively, a magnetic resonance imaging (MRI) was obtained at 1.5 T. Cine images showed a 1.3 cm measuring mass connected to the papillary chords (Panel A) without systolic prolapse. In the dark blood images (Panel B), the mass showed myocardial signal intensity. Delayed enhancement images 10 min post-Gd-administration demonstrated a hyperintense mass surrounded by a black rim isointense to the normal myocardium (Panel C). Surgery revealed a mass connected to the anterior chord of the papillary muscle. The histopathological examinations displayed a collapsed endocardium cyst, either because of a residual fibroelastoma or an endocardium defect with consecutive thrombotic changes (Panel D). The MRI offers the potential for differentiation between pathological processes by tissue-dependent signal characteristics. It may be suitable for pre-therapeutical decision-making. In conclusion, MRI was shown to identify non-invasively a regressive fibroelastoma as confirmed by histology.

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