Cardiovascular risk factors and aortic valve calcification: what do these associations mean?

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Aortic valve disease is the most prevalent valvular heart disease around the world, with degenerative aortic valve disease the most common aetiology in high-income countries. Both degenerative aortic valve disease and coronary artery disease share pathological features. In particular, the early stages of aortic stenosis, referred to as the initiation phase, demonstrate endothelial damage, lipid infiltration and inflammation leading to early valve fibrosis and calcification. It is perhaps therefore not surprising that risk factors for atherosclerosis have also been associated with incident aortic stenosis.

Khurrami et al present the results of the Danish cardiovascular screening trials (DANCASAVS I and II). They assessed a large cohort of 14 073 healthy men aged 60–74 years old, who were randomly selected from the Danish population. Calcification in the aortic valve and coronary arteries was assessed on non-contrast CT and associations with a variety of cardiovascular risk factors were investigated. In this asymptomatic elderly male population, aortic valve calcification was identified in 58% and coronary artery calcification identified in 83%. This high prevalence of disease is likely due to the age and gender of this cohort, with older patients having higher aortic valve calcium scores. Patients with more cardiovascular risk factors were more likely to have aortic valve calcification and had higher aortic valve calcium scores. In a multivariable analysis which included the presence of severe coronary artery calcification (>400 Agatston units, AU), only age, obesity, history of cerebrovascular disease and serum phosphate were independent predictors of the presence of aortic valve calcification.

Previous studies have attempted to unravel the complex interaction between aortic valve calcification, coronary artery calcification and cardiovascular risk factors. However, many of these studies have been limited because of the small sample size, single-centre nature and the use of cohorts of convenience undergoing assessment for symptoms of coronary artery disease. Recently, we reported in the multicentre Scottish Computed Tomography of the Heart (SCOT-HEART) trial, that in patients with stable chest pain, aortic valve calcification occurred in 14% and that the independent predictors of aortic valve calcification were age, sex, hypertension, diabetes mellitus and cerebrovascular disease. Other cohort studies have shown associations between different cardiovascular risk factors and the presence and severity of aortic stenosis or aortic valve calcification. However, the Epidemiology of Coronary Artery Calcium (ECAC) population demonstrated only a weak correlation between aortic valve and coronary artery calcification (r=0.35, p<0.01).

In the present study, Khurrami et al found that 90% of patients with aortic valve calcification also had coronary artery calcification, and 62% of patients with coronary artery calcification also had aortic valve calcification. However, they also only demonstrated a weak correlation between coronary artery calcification and aortic valve calcification (r=0.36; 95% CI 0.35 to 0.38; p<0.0001). Interestingly, the associations with some cardiovascular risk factors, such as hypertension and smoking, were stronger for coronary artery calcification than aortic valve calcification (figure 1). The diagnostic accuracy of using cardiovascular risk factors to identify patients with aortic valve disease was not particularly good. Having more than four cardiovascular risk factors identified patients with an aortic valve calcium score ≥300 AU with sensitivity of 72%, but a poor specificity of 56%. Therefore, there are other important, yet unknown factors, which drive the initiation and progression of aortic valve disease.

What are the prognostic implications of incident aortic valve calcification? Aortic stenosis and aortic sclerosis have been associated with an increased risk of cardiovascular events. Recently in the SCOT-HEART trial, subsequent cardiovascular events (cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke) were threefold more common in patients with aortic valve calcification than patients without. However, this association was not independent of the coronary artery calcium score or the presence of obstructive coronary artery disease and is therefore most likely mediated by coincident coronary atherosclerosis. Similarly, in the Multi-Ethnic Study of Atherosclerosis, which assessed 6685 asymptomatic patients, aortic valve calcification was associated with an increased risk of myocardial infarction and cardiovascular events, but not after adjustment for cardiovascular risk factors, inflammatory biomarkers and coronary artery calcium score. We look forward to further papers.

Figure 1  Aortic valve calcification and coronary artery calcification share overlapping risk factors, but whether this is due to association or causation remains uncertain.
from the DANCAVAS investigators to assess the prognostic implications of their findings which were not included in this analysis.

This manuscript also did not provide information on disease progression. Several studies have demonstrated that while atherosclerosis risk factors are associated with incident aortic stenosis, they are not associated with the asymptomatic phase of the disease and aortic stenosis progression. This is important when considering the development of novel aortic stenosis therapies that will need to slow disease progression rather than initiation if they are to be successful.

A very important limitation of this study is the inclusion of only male patients. Male sex has been identified as an important risk factor for the presence and severity of aortic valve calcification in multiple studies.

There are also differences in the pattern of aortic valve calcification between women and men, and potential differences in the compensatory response of the left ventricle to aortic valve stenosis.

Women develop more severe aortic valve stenosis at lower amounts of calcification than men, partly due to their smaller size but also related to a more prominent role for fibrosis in the pathogenesis. Thus, the aortic valve calcification thresholds for the presence of severe aortic valve stenosis are different in women and men.

More research is therefore required into sex differences in aortic valve disease in population-based studies.

In conclusion, this is by far the largest study to investigate the factors associated with incident aortic valve calcification, highlighting the common coexistence of atherosclerosis and aortic stenosis and their shared, overlapping risk factors. It makes a major contribution to our understanding of the initiation phase of aortic stenosis, overcoming many of the limitations of previous small single-centre studies and cohorts of convenience undergoing assessment for symptoms of coronary artery disease. More work is now required to investigate what we should do when incidental aortic valve calcification is identified in the asymptomatic general population. Addressing cardiovascular risk factors is an important part of their clinical care and in modifying their general cardiovascular health, although it is much less clear whether this has any effect on their valve disease per se. Identification of patients with advanced aortic valve calcification who may require more detailed echocardiographic assessment of their valve is also important, although clear thresholds as to when this should be performed remain to be defined. Khurrami et al have shown that aortic valve calcification is common disease in older male patients. Further work is required to determine how this should be treated, and in particular if we can halt progression and development of symptomatic disease.

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