The relationship between coronary artery spasm (CAS) and fixed atherosclerotic disease is controversial. In this issue of *Heart*, Kim and colleagues report outcome data at a median follow-up of 9.4 years for 3556 patients with symptoms (chest pain, sudden cardiac death or syncope) but no evidence of fixed epicardial coronary disease. Echocardiographic ergonovine coronary spasm provocation testing showed induced wall motion abnormalities consistent with CAS were in 23% of patients. Patients with CAS had significantly lower 10-year overall (90.5% vs 94.2%, p < 0.001) and percutaneous coronary intervention (PCI) free (97.4% vs 98.4%, p = 0.002) survival rates compared with those without CAS (figure 1). Although patients with CAS had higher frequencies of coronary risk factors, the presence of CAS remained an independent predictor of adverse outcomes even after adjustment by either Cox regression or Fine-Gray competing risk models.

In the accompanying editorial, McDermott and Bing point out that CAS is present in only a small proportion of patients who present with angina with non-obstructive coronary artery disease. In addition, diagnosis is challenging and there is little evidence to guide clinical management. Although ergonovine stress echocardiography is not widely available, studies from Korea have shown the safety of this approach in large patient series. McDermott and Bing conclude that the study by Kim and colleagues ‘provides important corroboration of a favourable long-term prognosis that is largely encouraging, as well as a gentle nudge to keep an open mind about the utility and application of tests or treatments with which we may be unfamiliar. The association between coronary vasospasm, the development of atherosclerotic coronary artery disease and future PCI is more difficult to disentangle. None will argue with the notion that vigilance in optimising cardiovascular risk factors and promoting good cardiovascular health are important goals that apply at least as much to a population of patients with coronary vasospasm as any other.’

In patients with asymptomatic moderate to severe aortic stenosis (AS), serum

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**Figure 1** Cumulative incidence of the primary and secondary endpoints. Cumulative incidence estimates for later PCI according to the presence of coronary artery spasm (A), for all-cause mortality (B), and for cardiovascular mortality (C). Major adverse cardiovascular events (D) were defined as all-cause mortality, myocardial infarction, stroke and later PCI. CAS, coronary artery spasm; PCI, percutaneous coronary intervention.

**Figure 2** In moderate to severe asymptomatic/minimally symptomatic aortic stenosis with preserved LV ejection fraction, MR-proADM most powerfully portended worse prognosis in single-biomarker models and was an integral component of the best double-biomarker models. Compared with MR-proADM singly, the best double-biomarker marker models with respect to the primary and secondary outcomes comprising MR-proADM and hSTNT or NT-proBNP performed no better than MR-proADM alone. GDF, growth differentiation factor; hSTNT, high-sensitivity troponin-T; MR-proADM, mid-regional proadrenomedullin; MR-proANP, mid-regional proatrial natriuretic peptide; NT-proBNP, N-terminal pro-BNP; LV, left ventricle.
biomarkers that predict outcome might allow individualised monitoring and optimisation of the timing of intervention. Tan and colleagues measured several known and novel biomarkers in 173 asymptomatic patients (mean age 69 years, 55% male) with at least moderate AS, defined as an aortic velocity of 3 m/s or higher or a valve area of 1.2 cm² or less, and normal left ventricular systolic function (ejection fraction 50% or higher). The primary combined outcome (all-cause mortality, heart failure hospitalisation or progression to NYHA classes III–IV) occurred in 34% at a median follow-up of 2.7 (1.4–4.6) years. Of the six biomarkers measured (figure 2), mid-regional proadrenomedullin (MR-proADM) had the highest discriminative value for the primary endpoint (subdistribution HR (SHR) 11.3, 95% CI 3.9 to 32.7).

Barton and Dweck comment that although symptom onset is the primary indication for aortic valve replacement in adults with AS, “there is increasing interest in more objective markers of LV dysfunction with which to optimise the timing of AVR. These include imaging markers of myocardial fibrosis and early systolic dysfunction as well as serum biomarkers such as high-sensitivity troponin and N-terminal-pro-beta natriuretic peptide (NTproBNP).” The data suggesting that MR-proADM may be a useful biomarker to predict prognosis in patients with AS is intriguing but further validation is needed along with studies of the relationship between this biomarker and left ventricular anatomy and function.

The BMJ recently published Rapid Recommendations for use of ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors for the reduction of cardiovascular events with one of the systematic reviews supporting those recommendations published in this issue of Heart. The recommendations apply only to adults with an elevated low-density lipoprotein cholesterol (LDL-C) (>70 mL/dL or >1.8 mmol/L) who are either already using a high-dose statin or are intolerant of statins. Recommendations are further stratified by the estimated 5 year risk of a major adverse cardiovascular event (MACE) categorised as low (<5%), moderate (5%–15%), high (15%–20%) or very high (>20 %) risk. As shown in figure 3, in patients already on a high-dose statin, adding a second agent is recommended only in those at high or very high risk.

Professor White puts these recommendations into the perspective that “Both PCSK9 inhibitors and ezetimibe have been shown to reduce LDL-C by approximately 60% and approximately 20%, respectively, and correspondingly may reduce MACE including all-cause death, cardiovascular death, myocardial infarction (MI) and stroke. However, the benefit of ezetimibe is small and PCSK9 inhibitors are very costly. Both drugs have adverse effects which must be considered when balancing recommendations to achieve maximal benefit and minimal harm.” He goes on to discuss the composition of the multiprofessional panel and the process used to generate these new recommendations. Problem and solutions for guideline development are presented in a detailed table. In addition, the BMJ Rapid Recommendations are compared with the European Society of Cardiology and American College of Cardiology/American Heart Association (ACC/AHA) guidelines and issues that should be considered in future guidelines are summarised. He concludes: “Let us hope that the recommendations are rapidly implemented worldwide.”

Also in this issue of Heart is a review article on the progression and management of calcific AS in patients with chronic kidney disease. Evaluation of AS severity can be challenging due to altered haemodynamics, often requiring integration of data from multiple imaging modalities.
Treatment considerations include a higher risk of early structural valve deterioration with a bioprosthetic valve and a higher bleeding risk with a mechanical valve, particularly when dialysis is needed. Management of these patients is optimised with a heart-kidney multidisciplinary team.

Air pollution is a major contributor to cardiovascular disease (CVD) risk, as summarised in a review article by Joshi, Miller and Newby in this issue. Potential mechanisms for the association between air pollution and CVD are discussed (figure 4). Prevention of air pollution related CVD can occur at the individual level, through use of masks and indoor air purification systems, and at the environmental level, through reduction in combustion-derived air pollutants. The authors conclude: “Air pollution has a staggering impact on global burden of morbidity and mortality, and is one of the leading modifiable risk factors for cardiovascular disease. Air pollution is a ‘silent’ pandemic deserving of an urgent and unswerving global effort to mitigate its effects. Stronger legislative measures to reduce air pollution and to encourage active travel will be rewarded with gains for both our environment and our health.”

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