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Kong, W.K.F.; Bax, J.J.; Delgado, V.

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EDITORIAL

Left ventricular myocardial fibrosis: a marker of bad prognosis in symptomatic severe aortic stenosis

William K.F. Kong [1,2]*, Jeroen J. Bax[1], and Victoria Delgado[1]

[1]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; and [2]Department of Cardiology, National University Heart Centre, National University Health System, Singapore

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This editorial refers to 'Impact of myocardial fibrosis on left ventricular remodelling, recovery, and outcome after transcatheter aortic valve implantation in different haemodynamic subtypes of severe aortic stenosis'[†], by M. Puls *et al.*, on page 1903.

Risk stratification of patients with severe aortic stenosis (AS) has been an important topic in the last years. Although symptoms and left ventricular ejection fraction (LVEF) remain crucial for decision-making,[1] several studies have shown other factors that may impact on the outcomes of patients with severe AS.[2–5] Classification of severe AS based on left ventricular (LV) stroke volume (flow) and mean transvalvular gradient has shown that patients with classical low-flow low-gradient severe AS (reduced LVEF) have the worst prognosis when treated with surgical aortic valve replacement or transcatheter aortic valve implantation (TAVI).[3–5] However, it is important to note that other studies have reported improvement in LV systolic function in patients with low-flow low-gradient severe AS regardless of the baseline LVEF.[5,6] Among 600 patients with low-gradient severe AS treated with TAVI, Schewel *et al.* demonstrated acute significant reduction in global afterload, and an increase in LV stroke volume index and left and right stroke work index in patients with paradoxical (preserved LVEF) and classical low-flow low-gradient severe AS.[5] However, these patients still had higher rates of all-cause mortality during follow-up as compared with patients with normal-flow low-gradient severe AS. When evaluating changes in LV systolic function at longer term follow-up after TAVI, several studies have shown that patients with low-flow low-gradient severe AS improve in LVEF and other parameters of LV systolic function. For example, in 68 patients with low-flow low-gradient severe AS (52% with reduced LVEF and 48% with preserved LVEF) treated with TAVI, Kamperidis *et al.* showed significant improvements in LV global longitudinal strain at 12 months of follow-up.[6] These studies nevertheless introduced a selection bias since patients have to survive for 1 year to demonstrate echocardiographic improvement in LV systolic function. Furthermore, not all patients present improvement in LV systolic function despite surviving 1 year after TAVI. Therefore, there are probably other parameters beyond the flow status and mean transvalvular gradient that may impact on the outcomes. Recently, the presence of extra-valvular damage such as severe mitral and tricuspid regurgitation, left atrial dilation and pulmonary hypertension, and right ventricular systolic dysfunction have formed part of a staging algorithm that is associated with prognosis in patients with severe AS treated medically, with surgical or transcatheter aortic valve replacement.[2,7,8] Many of these types of extra-valvular damage are a consequence of the response of the left ventricle to the pressure overload imposed by the stenotic aortic valve. Therefore, by evaluating the remodelling process of the left ventricle, we will eventually better understand the prognostic implications and the response to treatment.

Myocardial fibrosis is one of the pathophysiological factors involved in the LV remodelling process in severe AS. Histological studies have revealed that the transition from LV hypertrophy to heart failure in severe AS is driven by a combination of myocyte death and myocardial fibrosis.[9,10] Cardiovascular magnetic resonance (CMR) is the imaging modality that best shows replacement fibrosis, using late gadolinium enhancement (LGE), and estimates diffuse interstitial fibrosis with T1 mapping. Replacement myocardial fibrosis in patients with severe AS undergoing aortic valve replacement has been associated with persistent LV diastolic dysfunction and symptoms during follow-up, and with increased mortality (*Figure 1*).[11–13] In addition, it has been demonstrated that replacement myocardial fibrosis does not regress or resolve once the aortic valve has been replaced. Therefore, it could be hypothesized that referring patients with severe AS to aortic valve replacement before replacement myocardial fibrosis occurs would result in superior outcomes. However,

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* Corresponding author. Department of Cardiology, National University Heart Centre, National University Health System, Singapore. Tel: +65 6779 5555, Fax: +65 6779 5678, Email: william_kong@nuhs.edu.sg

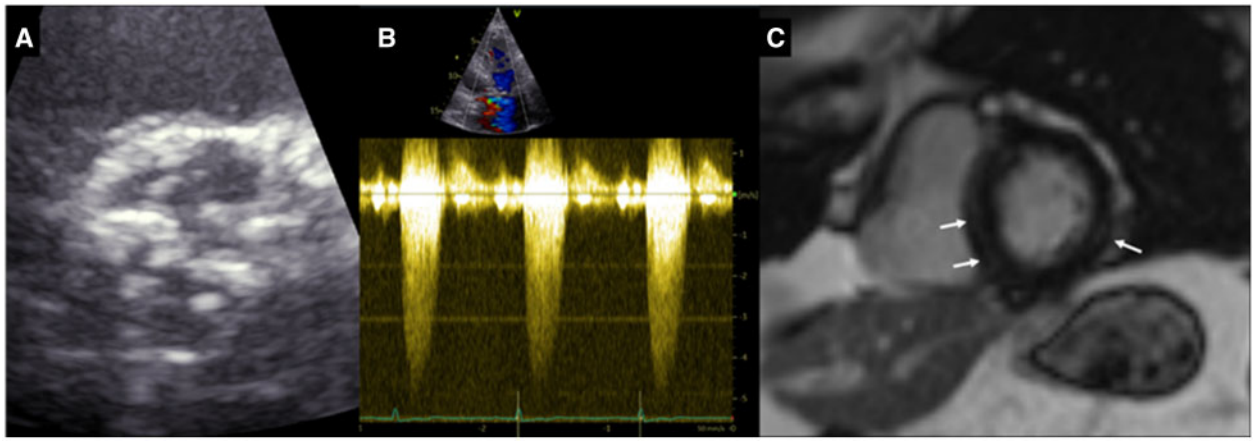

Figure 1 Myocardial fibrosis in severe aortic stenosis. Example of a 74-year-old patient with severe aortic stenosis. The aortic valve is tricuspid and severely calcified, with limited opening (*A*), causing a mean transvalvular gradient of 52 mmHg (*B*). On late gadolinium contrast-enhanced cardiovascular magnetic resonance, the left ventricular myocardium shows midwall delayed enhancement (arrows), indicating replacement myocardial fibrosis.

it has been shown that the presence of reactive interstitial fibrosis, which cannot be detected by LGE but by T1 mapping techniques, also portends a poor outcome.[10,14] In 400 patients with severe AS undergoing CMR before aortic valve replacement, Everett *et al.* demonstrated that increasing extracellular volume (a marker of reactive interstitial fibrosis) was associated with an increase in all-cause mortality (17.3, 31.6, and 52.7 deaths per 1000 patient-years across increasing tertiles of extracellular volume; log-rank test; $P = 0.009$).[10,14]

In the current issue of the *European Heart Journal*, Puls and co-workers present the results of a histological study including 100 patients with severe AS treated with TAVI.[15] Myocardial biopsies were obtained during the TAVI procedure and patients were divided according to the median value of myocardial fibrosis observed on histology studies (≥11% vs. <11% of the total tissue area) and according to the type of AS based on flow and gradient characteristics. Patients with classical low-flow low-gradient severe AS (n = 26) showed the most extensive myocardial fibrosis as compared with the other groups. It is important to note that there is significant overlap in terms of the extent of myocardial fibrosis across the groups and there is no significant difference between the patients with classical low-flow low-gradient AS and patients with reduced LVEF and a high transvalvular gradient. Interestingly, during follow-up, patients with myocardial fibrosis ≥11% had improvement in LVEF and regression in LV mass index comparable with those patients with myocardial fibrosis <11%. In terms of clinical outcomes, patients with myocardial fibrosis ≥11% had higher rates of all-cause mortality and cardiovascular mortality, confirming previous studies.[12,13] Nevertheless, myocardial fibrosis was not independently associated with all-cause mortality, whereas peripheral artery disease and atrial fibrillation were associated. This could be related to the relatively small patient population and the study could be underpowered to demonstrate the independent association between myocardial fibrosis and all-cause mortality as previous studies have shown.

Based on the cumulative evidence,[12–14] there is no doubt that the presence of myocardial fibrosis is associated with poor prognosis in patients with severe AS. However, all the studies include mostly patients with symptoms and reduced LVEF, and, therefore, class I indications for aortic valve replacement.[1] Assessment of myocardial fibrosis with LGE CMR or T1 mapping techniques will not change the management of these patients and, eventually, could be used to indicate in which patients TAVR would be futile. However, this was not the original hypothesis of the study. Ongoing trials evaluating the efficacy of aortic valve replacement in asymptomatic patients which include the assessment of myocardial fibrosis with LGE CMR could answer the question of whether earlier valve replacement is superior to a watchful waiting strategy [EARLY TAVR (NCT03042104) and EVoLVeD (NCT03094143)].

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