



Impact of sex on the management and outcome of aortic stenosis patients: a female aortic valve stenosis paradox, and a call for personalized treatments?

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Online publish-ahead-of-print 13 June 2021

This editorial refers to 'Impact of sex on the management and outcome of aortic stenosis patients', by D. Bienjonetti-Boudreau et al., doi:10.1093/eurheartj/ehab242.

The Forgotten Aortic Stenosis Patient



Aortic valve

AVA_i ≤0.6 cm²/m² (≤0.55cm²/m² if BMI≥30kg/m²)
and
Mean transvalvular gradient <40mmHg

Left ventricular morphology

Small LV end-diastolic diameters
Small LVOT
Low stroke volume

Female

Comorbidity profile

- Arterial Hypertension
- Small body size and overweight
- Normal coronary arteries
- HFpEF?

Graphical Abstract Typical profile of a contemporary aortic stenosis patient with excess mortality.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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Over the past decades, it has become clear that aortic stenosis (AS) represents a disease condition that differs in pathophysiology, presentation, and response to treatment between women and men. Even after accounting for body size, women need less valvular calcium than men to develop severe AS,¹ entailing sex-specific thresholds for computed tomography-derived aortic valve calcification used to identify severe AS.² Additionally, women with AS display more valvular fibrosis, denser connective tissue, and more concentric hypertrophy for a similar stenosis severity than men.³ Aortic valve replacement (AVR) is the only treatment option for patients with symptomatic severe AS, but sex-specific data on outcomes remain inconclusive. At the present time, it appears that women display a higher operative and long-term mortality, longer post-operative stay, and a higher stroke rate^{4,5} after surgical AVR (SAVR) potentially attributable to the more advanced stage of the disease at referral. In transcatheter AVR (TAVR) cohorts, women exhibit a higher incidence of vascular and bleeding complications with a trend towards a survival benefit over men after TAVR.^{6,7} These findings and data from a meta-analysis⁸ support the notion that TAVR appears to be the preferred intervention over SAVR in women when AVR is required—a hypothesis that is currently being tested in the RHEIA trial (NCT04160130). In this multicentre all-comers trial, female patients with severe symptomatic AS eligible for both AVR strategies based on a Heart Team decision are randomized 1:1 to receive TAVR or SAVR. Taken together, the overall impact of sex on the course and outcomes of AS is still under investigation.

In this issue of the *European Heart Journal*, Bienjonetti-Boudreau and colleagues focused on sex-specific differences in AS and their impact on clinical presentation and management.⁹ The authors studied a large cohort of 3632 consecutive patients with at least mild to moderate AS and distinguished four haemodynamic patterns according to indexed aortic valve area (AVAi) and mean transvalvular gradient (i.e. non-severe AS, severe AS, discordant high-gradient AS, and discordant low-gradient AS). After inverse propensity weighting, female sex could be linked to increased mortality and less referral to aortic valve intervention for the entire study population. This association was primarily driven by excess mortality observed in patients with discordant low-gradient AS defined as an AVAi $\leq 0.6 \text{ cm}^2/\text{m}^2$ ($\leq 0.55 \text{ cm}^2/\text{m}^2$ for patients with body mass index $\geq 30 \text{ kg}/\text{m}^2$) and a mean transvalvular gradient $< 40 \text{ mmHg}$. Women with discordant low-gradient AS who underwent initial medical management were at higher risk of mortality than their male counterparts, whereas no significant sex differences were observed in patients with discordant low-gradient AS who underwent aortic valve intervention.

Who are those female patients with ‘discordant low-gradient AS’?

We have summarized the typical profile of these patients in the *Graphical Abstract*. Up to 50% of all patients with severe AS are known to have low-gradient AS, which is either: classical low-flow low-gradient AS (LF-LG AS) and related to significant left ventricular dysfunction and low left ventricular ejection fraction

(LVEF); paradoxical LF-LG AS, where LVEF is preserved but flow is reduced; or normal-flow low-gradient (NF-LG) AS, where AVA is small combined with a low gradient, but normal flow. Because reduced LVEF was *a priori* excluded in the present study and aortic valve calcium scoring was not available, one might expect that a large proportion of those patients with discordant low-gradient AS may suffer from paradoxical LF-LG or NF-LG severe AS. As presented in table 3 of Bienjonetti-Boudreau *et al.*, echocardiographically estimated stroke volume indices were low in the presence of a normal LVEF, and somewhat more reduced in females than in males (34.65 ± 6.76 vs. $35.42 \pm 6.7 \text{ mL}/\text{m}^2$). Because AS is a disease of both the aortic valve and left ventricle,¹⁰ a closer look has to be taken at the left ventricle of these patients. While cardiac amyloidosis does not seem to show a higher prevalence in females,¹¹ other pathophysiological mechanisms may play a role. In a previous study by the same authors, it was shown that female sex is independently associated with a larger extracellular volume fraction and non-infarct pattern of late gadolinium enhancement, regardless of AS severity.¹² In females with AS, the left ventricles are characterized by advanced diastolic dysfunction with higher E/e' , and diastolic heart failure or heart failure with preserved ejection fraction is more common in elderly female patients, possibly due to a higher prevalence of arterial hypertension.

Why were women with discordant low-gradient AS referred less for AVR?

Women with LF-LG AS in TOPAS had similar outcomes to men in the medically managed subset but markedly higher mortality in the subset of patients undergoing AVR (hazard ratio: 1.82; 95% confidence interval 1.08–3.13; $P = 0.0248$).¹³ Did these data impact treatment decisions? Of course, information is missing on whether more females rejected AVR as they were older and potentially frailer. Information is also missing on the degree of valvular calcification that helps determine the likelihood of severe AS in patients with discordant low-gradient AS.²

In summary, we should be alerted by those female patients with low-gradient AS depicted in the *Graphical Abstract*, and ensure that (i) severe AS is not missed because of lower computed tomography calcium thresholds and (ii) a decision for medical therapy is fully justified, for example by patient choice or frailty. Still, in a large consecutive series of patients from a world-leading centre of valvular heart disease care, female patients with AS had higher mortality. This is paradoxical because while the proportion of persons who survive to age 90 years has been increasing over the study period in both sexes, women have been living longer than men in every Westernized birth cohort.¹⁴

Conflict of interest: G.G. has no conflicts to declare. I.M.L. has relationships with drug companies including AOPOrphan Pharmaceuticals AG, Actelion-Janssen, MSD, United Therapeutics, Medtronic, Neutrolis, and Ferrer. In addition to being an investigator

in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards.

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