

# Unveiling sex differences in valvular disease care and outcomes

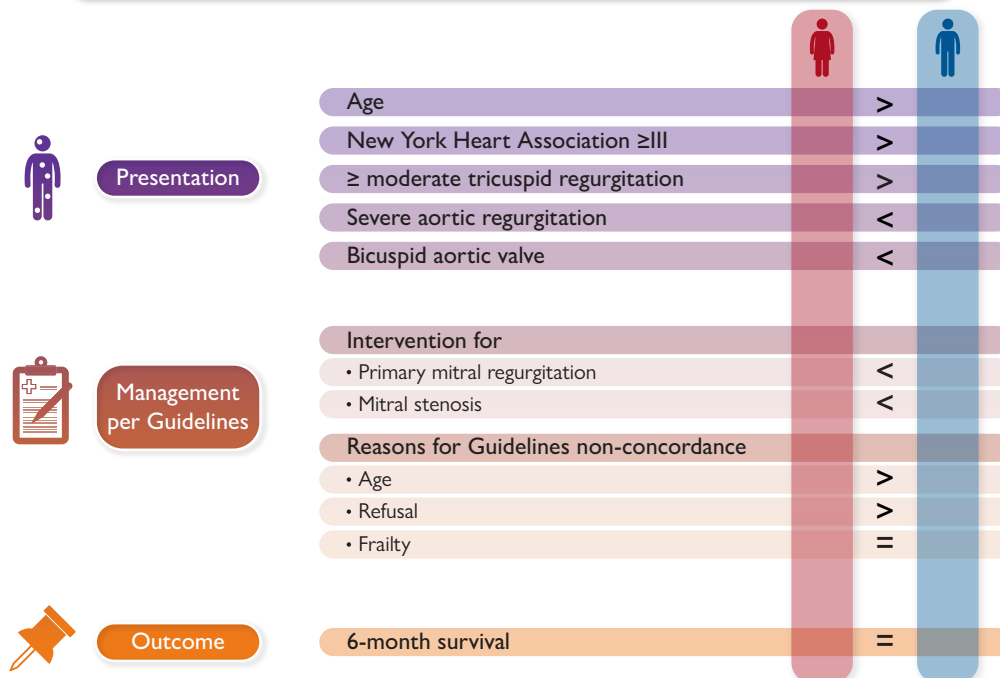
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This editorial refers to ‘Sex-related differences in severe native valvular heart disease: the ESC-EORP Valvular Heart Disease II survey’, by J. Mascherbauer et al., <https://doi.org/10.1093/eurheartj/ehae523>.

## Graphical Abstract

EORP VHD II: 5219 patients with native valvular heart disease



Valvular heart disease sex differences in presentation, management, and outcome. AR, aortic regurgitation; BAV, bicuspid aortic valve; EORP, EURObservational Research Programme; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; TR, tricuspid regurgitation

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Sex-related differences exist in valvular heart disease (VHD) on multiple levels, from anatomy, physiology, and pathophysiology to clinical outcomes.<sup>1,2</sup> The male and female left ventricles (LVs) adapt differently in response to similar changes in the haemodynamic and loading conditions.<sup>3</sup> The female LV tends to remodel concentrically, resulting in smaller LV cavity size and lower stroke volume, in contrast to eccentric remodelling in males.<sup>4</sup> It has been suggested that given a smaller LV, females might have a lower regurgitant volume and less pronounced ventricular dilatation in the presence of significant regurgitant lesions.<sup>5</sup> The female aortic leaflets have more fibrosis and less calcification than males for the same degree of aortic stenosis (AS) severity,<sup>6</sup> hence the need for gender-specific cut-offs for severe AS grading on computed tomogram. Women have smaller aortic annular sizes<sup>6</sup> and are at higher risk for patient–prosthetic mismatch than men. Women have smaller LV volumes and body surface area (BSA) but larger indexed LV volumes.<sup>7</sup> Consequently, when non-indexed LV dimensions are considered in severity assessment, women are less likely to meet the severity criteria that warrant surgery,<sup>7</sup> potentially resulting in late diagnosis and delayed intervention.

Differences in surgical outcomes between the sexes are notably worse for women than for men.<sup>5,8,9</sup> Studies on patients undergoing aortic valve surgery have shown that women tend to be older, have more advanced functional classes, and have higher surgical risk than men.<sup>8</sup> Not surprisingly, women are either referred late or less likely to be referred for aortic valve surgery.<sup>8</sup> Post-aortic surgery, women have a higher mortality rate compared with men.<sup>9</sup> In the COAPT trial, although there was no mortality difference between the sexes, women had more heart failure hospitalizations than men following transcatheter procedure.<sup>10</sup> There were, however, no sex differences in transcatheter aortic valve replacement outcomes.<sup>11</sup>

In this issue of the *European Heart Journal*, Mascherbauer and colleagues explored the differences between sexes in VHD frequency, management, and outcomes.<sup>12</sup> The study included 5219 patients with severe native VHD from the EORP VHD II survey. The study population was large, comprising 222 European and North African centres across 28 countries with diverse healthcare settings, allowing for contemporary, real-life data collection on guideline adherence. The 6-month mortality, i.e. cardiac and all-cause mortality, was reported. Both sexes were adequately represented, with a male-to-female ratio of 1.15. Analyses were stratified by sex and adjusted for EuroSCORE-II. Degenerative valve disease was the most common aetiology, and AS was the most common VHD in both sexes. Women were older and had more advanced functional classes and higher EuroSCORE-II. In contrast, men had higher rates of previous coronary interventions and more dilated LV cavities. The sex difference in the LV dimensions was no longer significant after indexing for BSA. Nearly half, i.e. 47.9%, of the patients received valve intervention within 6 months, with comparable frequency in both sexes. The management was concordant with Class I recommendations of the societies' guidelines for most valvular diseases, except for primary mitral regurgitation (MR) and mitral stenosis (MS), for which women were less likely to receive intervention after adjusting for EuroSCORE-II. The adjusted odds ratio (OR) of men with primary MR receiving intervention was 1.7 times higher than that of women. The adjusted OR of men with MS receiving intervention was 2.6 times higher than that of women. However, the latter should be interpreted with caution as the upper limit of the 95% confidence interval was 1.00 (*Graphical Abstract*).

Despite different healthcare usage patterns, the mortality did not differ between the sexes. Mascherbauer *et al.* reported no sex differences in the survival of patients treated conservatively or those who received

valve intervention. This differs from previous longer term studies that reported higher mortality in women compared with men, especially in the surgical cohort. Whether the survival difference would be apparent at longer term follow-up is beyond the scope of the present study. However, the lack of sex difference in the mortality rates may signal the narrowing of the gender gap in healthcare delivery in a contemporary, predominantly Western cohort. This is further substantiated by the finding that there was no sex difference in the number of patients treated conservatively due to economic barriers or resource limitations (14.4% of women and 15.4% of men,  $P = .673$ ).

Patient refusal, age, comorbidities, and frailty were the top four reasons for non-intervention in both sexes. Patient refusal was, by far, the most cited reason for non-intervention, i.e. in 48.1% of women and 34.3% of men. This suggests that the patient's decision for valve intervention is complex and multifaceted. From the patient's perspective, one's values, beliefs, and preferences often precede guideline recommendations in decision-making. This poses opportunities for innovative solutions, aiming at raising patient education and individualizing patient counselling that considers cultural and social contexts, empowering patients to make informed decisions. This also underscores the role of an interdisciplinary Heart Valve Clinic,<sup>13</sup> especially that of the nurse practitioner and primary physician, often the general cardiologist who has rapport with the patient.

Presently, the ESC and ACC/AHA guideline-derived cut-off values for LV dimensions for mitral valve surgery are neither indexed to body size nor sex specified, potentially disadvantaging people of smaller build as the severity could be underestimated. Whether this could explain the reduced odds of women receiving intervention for primary MR and MS is beyond the scope of this study. This study, nevertheless, challenges the VHD community to re-examine the status quo. Apart from indexing for BSA and having gender-specific cut-offs, there could be more reliance on volume- and flow-independent measures of valve severity, such as indexed valve area in stenotic lesions and regurgitant fraction in regurgitant lesions in men and women of extreme sizes.

The main limitation of this study is the lack of longer term follow-up. The survey concluded in 2017, and the societies' guidelines have since been updated to include recommendations on percutaneous therapies. Thus, the uptake of percutaneous treatment is likely to be significantly higher in present-day cardiology practice. Two caveats should be kept in mind when interpreting the results. First, multiple comparisons made were not corrected for some bias; some results could be significant by chance. Second, the variables in the regression models, i.e. sex and EuroSCORE-II, are correlated, as sex is a factor in EuroSCORE-II calculation. However, the degree of correlation between these two variables and its impact on result interpretation is unclear.

This study outlines sex differences in VHD phenotypes that affect multiple fronts, from disease screening to healthcare provision. Whilst intriguing, the biological mechanisms underpinning sexual dimorphism remain elusive, warranting further basic and translational research. Sex is an intrinsic, traditionally non-modifiable variable. What can be acted upon are modifiable sex differences, such as systematic and scientific biases. The cardiology community should strive to close the gender data gaps by promoting studies that embrace diversity and inclusion in the enrolment or analyses, such as the present study. The *European Heart Journal* should be applauded for championing representation in cardiovascular research, for data are a persuasive and unambiguous argument in the fight for equality.

Three decades after Dr Bernadine Healy first described the Yentl syndrome,<sup>14</sup> the cardiology community has made progress in diagnosing and managing ischaemic heart disease in women. However, gender

data gaps still exist in many areas of cardiology, including VHD, heart failure, electrophysiology, and cardiometabolic disease; thus, closing the gender data gaps in cardiovascular research remains a work in progress. Ultimately, we strive for equitable healthcare, where sex or gender equality is an important but not the sole determinant. The holy grail should be the representation of women (and men) of different races, ethnicities, and socioeconomic backgrounds in cardiovascular research to help us better understand health behaviours and needs at the intersections of these identity dimensions.

## Declarations

## Disclosure of Interest

The authors declare no disclosure of interest for this contribution.

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