



Published in final edited form as:

*Am Heart J Plus.* 2022 September ; 21: . doi:10.1016/j.ahjo.2022.100197.

## Sex differences in aortic stenosis: Identification of knowledge gaps for sex-specific personalized medicine

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### Abstract

**Objectives:** This review summarizes sex-based differences in aortic stenosis (AS) and identifies knowledge gaps that should be addressed by future studies.

**Background:** AS is the most common valvular heart disease in developed countries. Sex-specific differences have not been fully appreciated, as a result of widespread under diagnosis of AS in women.

**Summary:** Studies including sex-stratified analyses have shown differences in pathophysiology with less calcification and more fibrosis in women's aortic valve. Women have impaired myocardial perfusion reserve and different compensatory response of the left ventricle (LV) to pressure overload, with concentric remodeling and more diffuse fibrosis, in contrast to men with more focal fibrosis and more dilated/eccentrically remodeled LV. There is sex difference in clinical presentation and anatomical characteristics, with women having more paradoxical low-flow/low-gradient AS, under-diagnosis and severity underestimated, with less referral to aortic valve replacement (AVR) compared to men. The response to therapies is also different: women have more adverse events with surgical AVR and greater survival benefit with transcatheter AVR. After AVR, women would have more favorable LV remodeling, but sex-related differences in changes in myocardial reserve flow need future research.

**Conclusions:** Investigation into these described sex-related differences in AS offers potential utility for improving prevention and treatment of AS in women and men. To better understand sex-based differences in pathophysiology, clinical presentation, and response to therapies, sex-specific

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. C. Noel Bairey Merz, serves as Board of Director for iRhythm, fees paid through CSMC from Abbott Diagnostics and Sanofi. Dr. Janet Wei served on an advisory board for Abbott Vascular. All other authors have no other conflicts of interest to report.

critical knowledge gaps should be addressed in future research for sex-specific personalized medicine.

## Keywords

Sex; Aortic stenosis; Cardiovascular disease

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## 1. Introduction

Aortic stenosis (AS) is the most common valvular heart disease in developed countries [1]. While AS has long been associated with aging, sex-specific differences have not been fully appreciated, as a result of widespread under diagnosis of AS in women [1].

However, more recent evidence suggests that the incidence of AS in older patients (>75 years of age) is in fact higher in women compared to men [2].

In AS, as in many cardiovascular disorders, women and men differ due in part to anatomical and physiological differences. Indeed, biological sex is known to impact cardiac remodeling and fibrosis in AS [3,4]. Moreover, women have increased risk of adverse events after surgical aortic valve replacement (AVR) [5], and being woman is a risk factor in the commonly used Society of Thoracic Surgeons (STS) score [6].

The objective of this review is to summarize the current evidence of sex-based differences in AS and identify knowledge gaps that should be addressed by future studies.

## 2. Pathophysiology

Aortic stenosis is the late result of an inflammatory process leading to aortic valve calcification (AVC), fibrosis and changes in the myocardium in response to pressure overload. There are important differences between men and women in the anatomy and adaptive pathophysiology to AS which we summarize here.

### 2.1. Aortic valvular calcification

AVC is the primary pathophysiological mechanism of AS. The AVC score by Multislice Computed Tomography (MCT) correlates strongly with the calcium weight of aortic valve, being the gold standard method to measure it [7]. There are sex differences in AVC measured by MCT: sex-specific Agatston units thresholds for diagnosis of severe AS are lower in women (1300) compared to men (2000) [8]. Women tend to have less calcification and more fibrosis deposits on their aortic valve [9]. For similar amounts of AVC, women reach hemodynamically more severe AS, even after adjusting for smaller body surface area [9–12]. This reflects the contribution of leaflet fibrosis and calcification to increased leaflet stiffness in women.

In the pathophysiology of AVC, inflammation, lipoprotein profiles, and matrix remodeling are the main factors involved in the calcification process [13]. The impact on sex is poorly understood, but the molecular mechanisms proposed for AVC underlying differences between sexes appear to be the following (Fig. 1):

- IFN- $\alpha$  activity alone, and in combination with lipopolysaccharide, triggers higher inflammation and calcification in male aortic valve interstitial cells (VICs) compared to females, by a higher secretion of prostaglandin E<sub>2</sub>, Interleukin-6 and interleukin-8 [14,15].
- Female-specific phosphorylation of Akt — a kinase reported to play a role in aortic VICs calcification [13,15] — lowers interleukin-6 secretion in female aortic VICs, protecting interstitial cells from mineralization [14].
- Difference in gene expression profiles between men and women. To date, 183 genes have been identified as being significantly different in male versus female aortic valve leaflets [16,17]. These gene expressions are implicated in different biological processes linked to calcification, including cellular proliferation, apoptosis, migration, ossification, angiogenesis, inflammation, and extracellular matrix reorganization [16]. Males are associated with upregulation of bone sialoprotein 2 (BSP2), runt related transcription factor-2 (RUNX2), osteocyte marker sclerostin (SOST) and tissue nonspecific alkaline phosphatase (TNAP) genes, and downregulation of the mineralization inhibitor matrix-Gla protein (MGP) [14]. The effect of the different gene expression in male aortic VICs makes them more prone to apoptosis, with secondary dystrophic calcification [18], explaining the higher degree of AVC in men than in women found in clinical trials.

## 2.2. Aortic valvular fibrosis

In response to stress or injury, VICs (fibroblasts) become activated to myofibroblasts, which is associated with extracellular matrix remodeling and contributes to valve fibro-calcification [19]. As we mentioned before, compared to men, women have more fibrous collagen in their aortic valves [10,11]. Mechanisms underlying sex-related differences in fibrosis include different gene expression profiles and phenotypes [16], causing elevation of  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) and increased myofibroblast activation in VICs of female aortic valves, compared to male aortic valves [20].

## 2.3. Left ventricular (LV) response to pressure overload

Men and women appear to develop different patterns of LV remodeling and myocardial fibrosis [3,4]. Compared to men, even with the same degree of valvular stenosis, women tend to develop a more restrictive physiology pattern with concentrically remodeled and subsequent concentric LV hypertrophy and less dilated left ventricle, whereas men present with more dilated and eccentrically remodeled left ventricle [3,4] (Fig. 2).

Women have greater LV relative wall thickness, smaller LV cavity volumes and dimensions, higher estimated LV filling pressures (related to reduced LV compliance), and more advanced LV diastolic dysfunction [4]. In addition, according to studies with CMR comparing LV ejection fraction (LVEF) between women and men in the general population, women had a higher LVEF compared to men; and the threshold value to define low LVEF was below 61 % in women and below 55 % in men [21]. This may affect thresholds used to make therapeutic decisions in asymptomatic patients with severe AS.

Depending on the stage of AS evaluated and the imaging modality used, variable sex-differences in AS have been reported. Studies with echocardiography in severe AS have shown that women have more concentric LV hypertrophy [4]. In contrast, studies with cardiovascular magnetic resonance (CMR) — a method that gives a more accurate assessment of LV chamber size and morphology and has the ability to identify myocardial fibrosis — have shown a trend toward less concentric LV hypertrophy, more concentric LV remodeling and lower LV mass index in women compared to men [3,22]. Despite women having a smaller LV mass index, compared to men, they have larger extracellular volume (ECV) fraction (measured noninvasively by CMR T1 mapping) and similar non-infarct pattern of late gadolinium enhancement (LGE, also a noninvasive CMR measure), regardless of AS severity [22]. Whereas LGE represents irreversible focal fibrosis, ECV represents a potentially reversible diffuse pattern of interstitial fibrosis that occurs at an earlier stage of the disease [22] (Fig. 3). More work in this area is still needed, however, because while CMR-derived ECV correlates with collagen content [23,24], it is possible that the larger ECV fraction in women could be related to others factors like greater capillary density [25]. This could explain why AS studies that have taken biopsies report different results than CMR derived ECV [24].

The molecular mechanisms underlying differences between sexes are not completely understood; differences in fibrosis regulatory pathways could partially explain sex-related differences (Fig. 4). In men myocardial fibrosis appears to be mainly driven by AS severity and extent of LV hypertrophy, whereas in women, the remodeling, hypertrophy, and fibrosis are more heterogeneous and multifactorial.

In males' fibrosis is also associated with sex hormones: both testosterone [26] and 17 $\beta$ -estradiol, which mediates its effect via estrogen receptor activation, resulting in increased deposition of collagen I and III in men compared to females [27]. In addition, the renin-angiotensin-aldosterone system (RAAS) activation plays a greater role in males compared to females, since estrogen downregulates angiotensin 1 [28].

Response to AS overload in women appears to depend more on: 1) genetic factors as matrix-related gene expression [16,29]; 2) a preferential transcriptional activation of collagen I over other extracellular matrix components in the myocardium [27,29]; 3) polymorphism in the estrogen receptor in postmenopausal women with chronic RAAS activation [30]; and 4) a functional polymorphism of the renalase (RNL) gene — an enzyme which protects tissues of adrenergic activation, decreasing circulating catecholamines that promotes hypertrophy of cardiac myocytes and hyperplasia of cardiac fibroblasts [31].

Differences in sex-specific cardiac remodeling may also be explained by more cardiomyocyte loss (apoptosis) in males than females, resulting in more of an eccentric pattern of hypertrophy vs females who have more a concentric hypertrophic pattern [32,33].

There are very limited data on the impact of the different types of remodeling on clinical outcomes and prognosis in AS. From the limited information available, concentric remodeling and hypertrophy appear to be independently associated with all-cause and cardiovascular mortality [34]. Indeed, among women with AS and preserved LVEF, the

impact of concentric hypertrophy on prognosis is worse (60 % increased risk) than in men [34]. We have elaborated on adverse sex-specific relationships between patterns of left ventricular remodeling and clinical outcomes in women previously [35].

The exact mechanism linking concentric remodeling with worse outcomes in women remains incompletely understood. Subendocardial ischemia may represent one potential mechanism, due to oxygen supply/demand mismatch of the hypertrophied myocardium, reduced diastolic perfusion time, coronary microvascular dysfunction and low coronary perfusion pressure [36–38]. Indeed, basal blood flow is higher in the hypertrophied myocardium (i.e. increased baseline blood flow velocity), while hyperemic flow is reduced, resulting in a reduction of myocardial perfusion reserve (MPR) – a measure of microcirculatory function. Impaired MPR, as a marker of microvascular dysfunction, is an independent predictor for future cardiovascular events in AS [39–42], and seems to be a key contributor to the transition from adaptive to maladaptive LV remodeling [42]. However, when using echocardiography to measure aortic valve area (AVA), CMR to assess LV mass, and positron emission tomography to quantify resting and hyperemic myocardial blood flow and coronary vasodilator reserve, a correlation between LV mass and MPR is not always found in AS [39,43]. Likewise, LV mass did not relate to MPR when derived from stress CMR in patients with severe AS [40]. Interestingly, a correlation between impaired MPR and female sex, myocardial fibrosis and filling pressure was observed in this later investigation. However, these results were collected in a relatively small number of predominantly male participants. This correlation has not been much studied in a sex-specific manner in AS, emphasizing the need for further sex-specific investigation in this area.

### 3. Clinical presentation

Recently, description addressing sex differences in the clinical presentation of AS has increased [2,44–46]. For the same aortic valve area and hemodynamic impairment, women are older at presentation, with lower body mass index, higher frailty score of 2 to 3, lower glomerular filtration rates and higher anemia rates [5,44–46]. Compared to men, women have a higher prevalence of hypertension and diastolic dysfunction, less coronary artery disease [46], with an overall higher surgical risk profile [45,46]. Obesity in AS is associated with increased mortality in women and men, although it is less of a factor in older women with AS who are more often lean [47,48].

Women hearts and their aortic annuli/aortic roots tend to be smaller, and concomitant mitral and tricuspid valve disease is substantially more common [45,46]. The older age and higher prevalence of hypertension in women both lead to reduced systemic arterial compliance. Lower systemic arterial compliance in AS is typically associated with older age and women, and is also independently associated with impaired prognosis [49]. Interestingly, although having a higher normal value for LVEF, women have a lower stroke volume index and a reduced flow rate across the valve [50], an entity called ‘paradoxical low-flow low-gradient AS’. This entity seems to be more prevalent in women than men [51]. Importantly, this AS entity has a worse prognosis with medical treatment, higher operative mortality and long-term postoperative mortality [52].

At the time of diagnosis of AS, women have more advanced New York Heart Association (NYHA) class symptoms [44,53,54]; with a shorter exercise duration and lower anaerobic threshold [55]. Women have a trend toward a greater symptomatic presentation with shortness of breath and dizziness/syncope [45,46,56]. Probably explained by their greater prevalence of microvascular dysfunction, higher frequency of concomitant tricuspid/mitral valvular disease, smaller LV cavity and lower LV mass with diastolic dysfunction.

#### 4. Diagnosis of aortic stenosis

Compared to men, women with severe AS are older and with more atypical symptoms, such as dyspnea and dizziness. They tend to perceive their cardiac disease as less severe, they are more hesitant at the time to undergo a diagnostic procedure, and they are less referred to a specialist undergoing fewer diagnostic tests [57,58].

Furthermore, the higher prevalence of hypertension, smaller aortic root, smaller LV cavity with smaller stroke volume index and lower flow rate [45,46,50], and higher prevalence of paradoxical low-flow low-gradient AS in women [51] contribute to the accuracy of AS diagnosis and severity grading. Besides, the lack of sex-specific cut-off values for identification of low stroke volume [21], make an accurate diagnosis of AS in women challenging.

Thus, these clinical challenges in women at the time of AS grading/diagnosis may explain the under diagnosis and underestimation of AS severity in women. This is a key reason for which women are referred later than men for intervention.

#### 5. Treatment options and outcomes

Without treatment, severe symptomatic AS has a poor prognosis, with most patients dying 2–3 years after diagnosis [59,60]. To date, no medical treatment has been shown to slow AS progression [61–65]. The only definitive treatment option for severe AS is the aortic valve replacement (AVR), either surgically or transcatheter approach [66–68]. Current guidelines recommend intervention in patients who are symptomatic or asymptomatic but in the presence of LV dysfunction or with symptoms/sustained fall in blood pressure in an exercise test [8,69]. As we mentioned before, the normal reference values for LVEF are higher in women compared to men [21]. Thus, the threshold LVEF defining LV dysfunction in women may need to be revised when making clinical decisions about treatment in asymptomatic AS.

##### 5.1. Selection of surgical aortic valve replacement (SAVR) vs transcatheter aortic valve replacement (TAVR)

Overall, selecting the optimal therapy for women with severe AS between SAVR and TAVR, depends on their anatomy and risk profile. Recent data has shown that the risk of 5-year mortality after diagnosis of severe AS was greater in women than in men, explained by a more conservative AS management in women [53]. Compared to men, women appear to be less frequent and later referred to AVR than men, being older and at a later stage of the disease [53,70].



Women's representation in the most relevant interventional trials in AS is better than in cardiovascular disease clinical trials in general. However, women's inclusion in most of these studies is still under 50 % (Table 1).

Although women are at an increased risk for adverse events after SAVR [5,6,71–73], and have greater survival benefit with TAVR [44,74–80], these results were never confirmed by a specific trial in women. Despite none of these trials did randomize on the basis of gender, women are more likely to undergo a TAVR procedure. This is confirmed by data from TVT Registry and European Registry, where women account for about 50 % of patients undergoing TAVR [78].

## 5.2. Short-term events and survival outcomes data

After TAVR, there are no differences in in-hospital and 30-day mortality rates between sexes [71,77,78]. However, as a result of having less aortic valve calcification and a smaller annular size, women are less likely to develop paravalvular regurgitation, which is an important determinant of prognosis following TAVR [88]. The procedure related complications, including bleeding and device related complications, strokes events as well as conversion to conventional SAVR, are more common in women [74,75,78,79,89]. These could be related to several factors, such as a smaller body area with smaller-caliber peripheral arteries, smaller aortic annulus and aortic root [90], higher rates of porcelain aorta and hormonal influences on vascular biology [91]. On the other hand, women with smaller aortic annulus, would have a possible benefit of TAVR over SAVR, due to less prosthesis-patient mismatch [92] — particularly in combination with paradoxical low flow, low gradient severe AS — which significantly increases the risk of mortality [93]. There are conflicting results of the sex differences on pacemaker implantation after TAVR [94]. According to a recent meta-analysis of 70,000 patients, the risk of post TAVR pacemaker implant is 10 % lower in women compared to men [95].

Alarming, studies assessing the impact of sex on outcomes of SAVR provide conflicting results suggesting that women have worse outcomes for mortality (in-hospital and 30-day mortality rates), stroke, and postoperative stay than men [6,70,96]. A recent review suggests that SAVR is associated with an increased risk of 30-day mortality in women compared to men [97]. The same as TAVR, anemia, vascular complications, bleeding or blood transfusion is also more common in women than men undergoing SAVR [44]. Women also have more renal and heart failure [71], and higher transvalvular gradients with higher prosthesis-patient mismatch [92] (Fig. 5).

More research with randomized clinical trials on the basis of gender is clearly needed to better understand the pathophysiologic mechanisms driving sex-specific outcomes.

## 5.3. Long-term events and survival outcomes

Women seem to have a better long-term survival after TAVR compared to men. Compared with women undergoing SAVR, female TAVR patients have lower major stroke and lower 1-year/2-year mortality [44,97,98].

Sex differences in reverse remodeling after AVR have been studied. Women with AS have more diffuse fibrosis, though they appear to respond more favorably to AVR than men. After both SAVR and TAVR, women have less myocardial fibrosis, more favorable LV remodeling and faster regression of LV hypertrophy than men [99,100]. On the other hand, women with maladaptive LV hypertrophy have worse survival after AVR than women with adaptive LV hypertrophy; in contrast to men, where the pattern of LV hypertrophy did not affect survival [99]. However, sex-specific studies with CMR in this area are necessary to better assess LV mass post AVR and confirm these results.

Although an active area of investigation, lower expression of periostin [99] — a key regulator of cardiac fibrosis — and fast changes in protein synthesis [100], likely contribute to the lower fibrosis (linked to an adaptive LV hypertrophy) and regression of ventricular remodeling in female hearts after AVR.

Even following indications of treatment of AS by current guidelines, a significant proportion of patients, predominantly women, experiences persistent dyspnea after AVR. In the PARTNER II trial, 30 to 40 % of surviving patients remained in NYHA class II or more 2 years after TAVR or SAVR and can be considered as heart failure with preserved ejection [83]. Data from the WIN-TAVI Registry — the first “real world” all females registry examining outcomes following TAVR [101] — showed an increased incidence of hospitalizations for heart failure or valve-related symptoms during 1-year follow-up in women. They also demonstrated that 36.4 % of women remained in NYHA class II/IV 1 year after TAVR. While the exact mechanism for sex-specific symptoms in women remain incompletely understood, we hypothesize that the higher incidence of microvascular dysfunction and persistent diastolic dysfunction in women likely play an important role [38,102]. Indeed, elevated interleukin-6 strongly predicted heart failure hospitalization and all-cause mortality in women with coronary microvascular dysfunction, suggesting that inflammation plays an important role in the pathogenesis [102]. Prospective serial CMR anatomical, perfusion, and T1 imaging with serial inflammatory biomarkers analyzing sex-related differences are therefore needed to determine unresolved mechanisms contributing to persistent symptoms, reduced quality of life, and frequent hospitalization in patients after TAVR.

## 6. Summary and identification of knowledge gaps

A better understanding of sex-related differences in AS could lead to improved risk stratification schemes, optimized timing of intervention, and formulation of sex-specific prevention and treatment plans. The Central illustration summarizes most relevant sex-related differences in AS, including pathophysiology, anatomy, clinical presentation and clinical outcomes after treatment. As demonstrated in Table 1, women are underrepresented in most interventional AS trials, and the extrapolation of these results to women could be inappropriate. This highlights the need of further research specifically in women, like the currently ongoing RHEIA (Randomized researchH in womEn all Comers Aortic stenosis) Trial [103], evaluating safety and efficacy between TAVR and SAVR in female patients with severe symptomatic AS.



Investigation into these described sex-related differences in AS offers potential utility for improving prevention and treatment of AS in women and men. To better understand sex-based differences in pathophysiology, clinical presentation, and response to therapies, the knowledge gaps summarized in Table 2 should be addressed in the future research for sex-specific personalized medicine.

Updating prior articles on this topic [80,104], this review article of sex-related differences in important aspects of the aortic stenosis highlights the lack of existing evidence and knowledge gaps, identifying needs for sex-specific investigation and clinical trials.

## Funding

This work was supported by the National Institutes of Health R01HL124649, U54 AG065141, the Eli and Edythe Broad Foundation and the Constance Austin Women's Heart Research Fellowships, Cedars-Sinai Medical Center, Los Angeles, California, the Barbra Streisand Women's Cardiovascular Research and Education Program, Cedars-Sinai Medical Center, Los Angeles, The Society for Women's Health Research (SWHR), Washington, DC, the Linda Joy Pollin Women's Heart Health Program, the Erika Glazer Women's Heart Health Project, and the Adelson Family Foundation, Cedars-Sinai Medical Center, Los Angeles, California.

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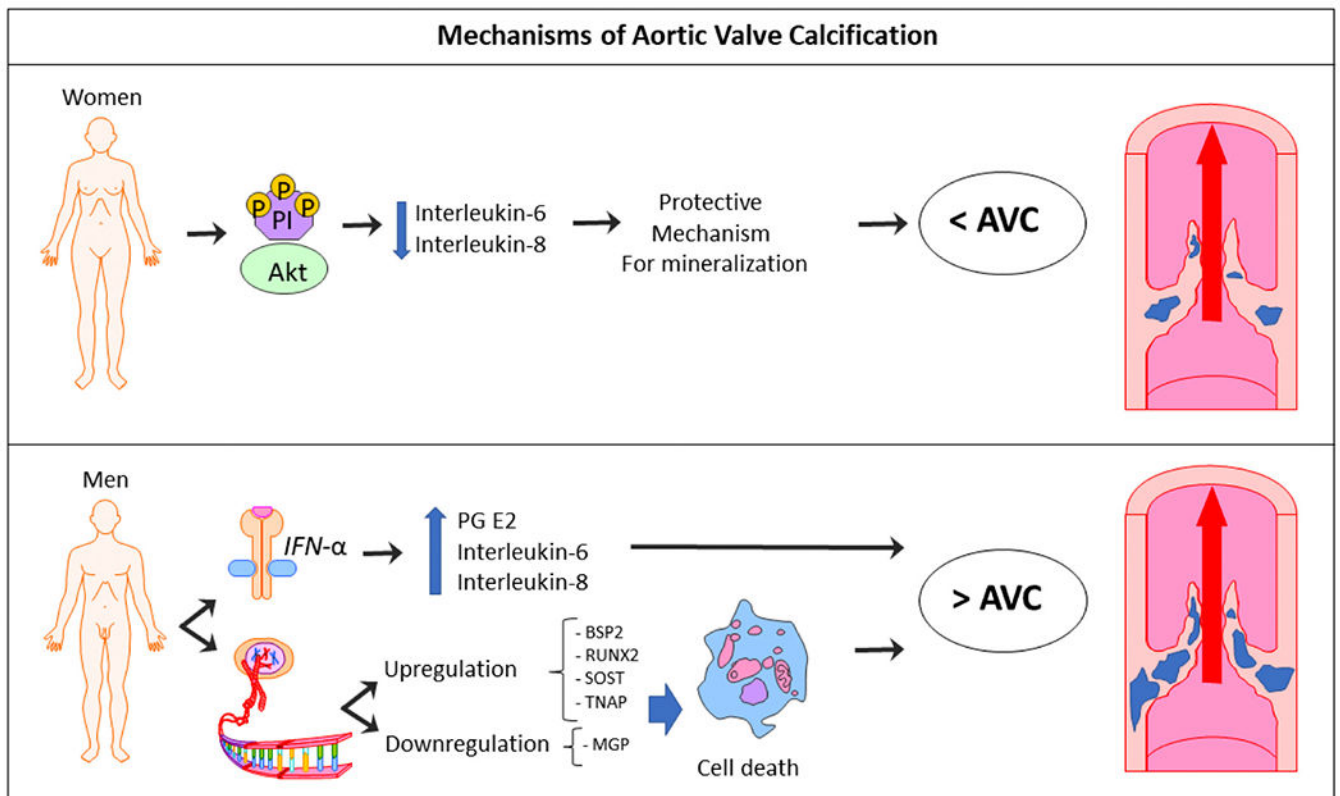


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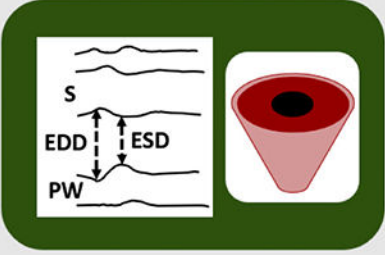
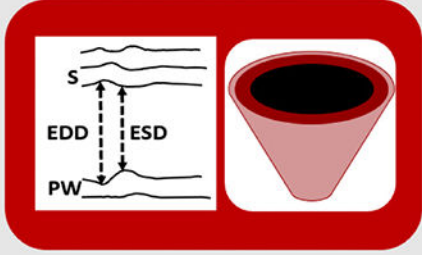
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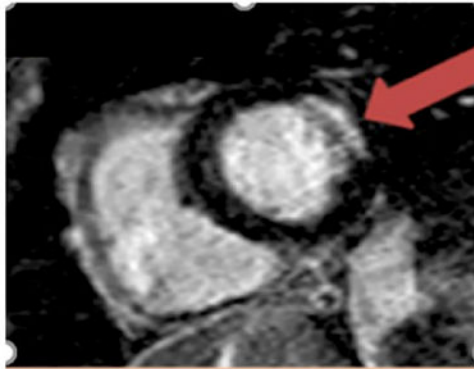
**Fig. 1.** Mechanisms of aortic valve calcification (AVC).

(Abb.: Akt = kinase; PI = phosphorylation; IFN- $\alpha$  = interferon alfa; PG E2 = prostaglandin E2; BSP2 = bone sialoprotein 2; RUNX2 = runt-related transcription factor-2; SOST = osteocyte marker sclerotin; TNAP = tissue nonspecific alkaline phosphatase; MGP = mineralization inhibitor matrix-Gla protein.)

WOMEN		MEN
<p>+++ Concentric Remodeling</p> 	<p>Type of Geometric Pattern</p>	<p>+++ Eccentric Remodeling</p> 
<p>&gt; 0.42</p>	<p>Relative Wall Thickness</p>	<p>≤ 0.42</p>
<p>&lt; 95 g/ m<sup>2</sup> BSA</p>	<p>LV Mass Index</p>	<p>&gt; 115 g/m<sup>2</sup> BSA</p>

**Fig. 2.**  
 Sex-related differences in geometric patterns of LV response to pressure overload.  
 Patterns of cardiac remodeling according to relative wall thickness and LV mass index.  
 Each type of LV geometry is illustrated by lines representing M-mode images.  
 (Abb.: LV = left ventricle; S = septum; EDD = end-diastolic diameter; ESD = end-systolic diameter; PW = posterior wall.)

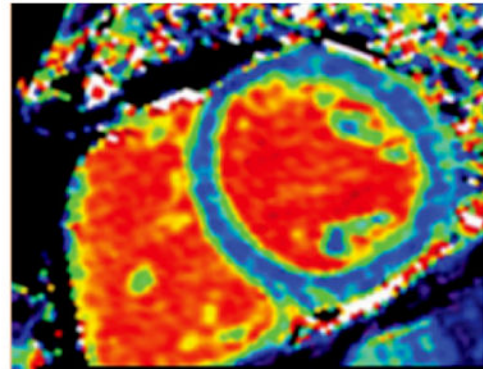
## Myocardial fibrosis in CMR



LGE



No differences between  
women and men



ECV T1 mapping



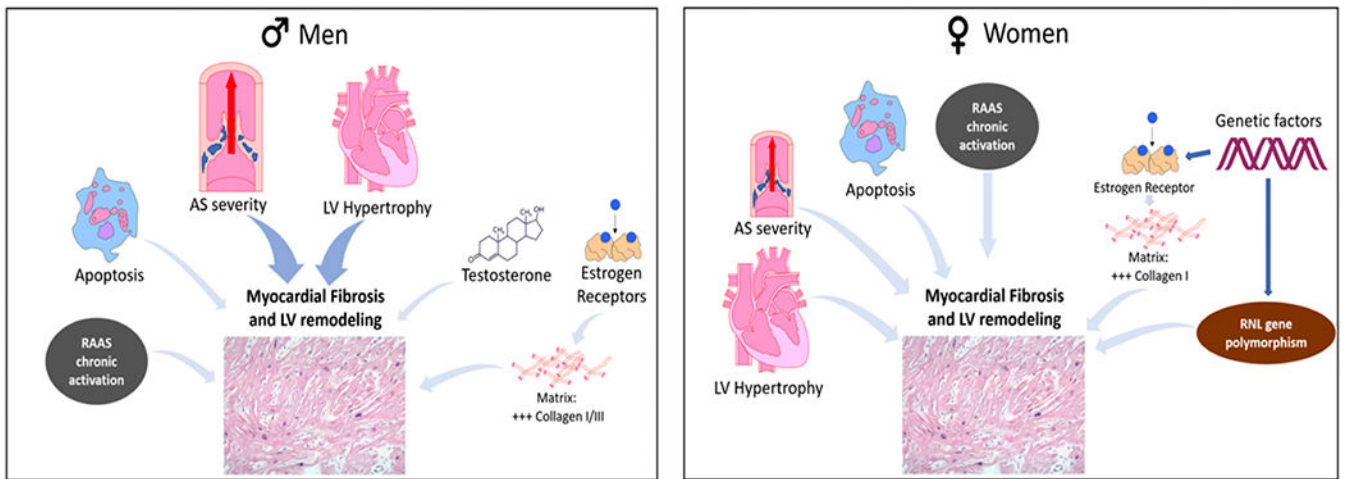
ECV > women compared to  
men

**Fig. 3.**

Sex differences in expansion of myocardial fibrosis in aortic stenosis.


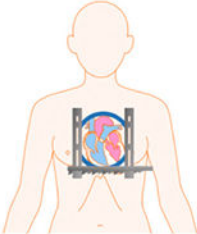
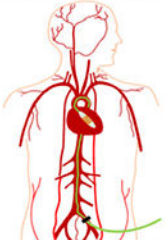
Compared to men, women have similar amounts of replacement myocardial fibrosis (=LGE) and larger extent of diffuse myocardial fibrosis (=ECV).

(Abb.: CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; ECV = extra cellular volume.)

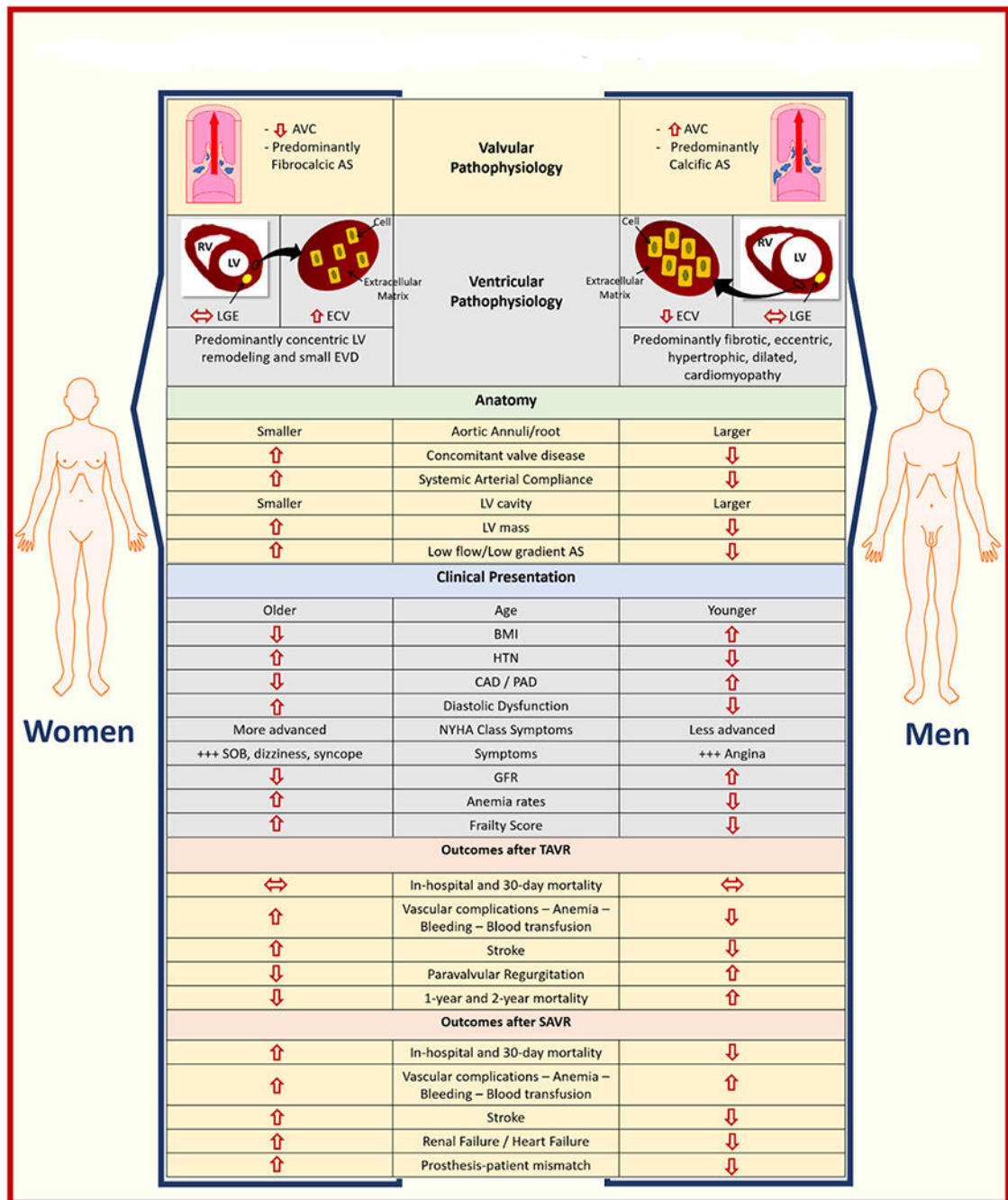


**Fig. 4.** Molecular mechanisms underlying myocardial fibrosis and LV remodeling. Myocardial fibrosis: in men, mainly driven by LV hypertrophy and AS severity, and more cardiomyocyte loss but in women the response to pressure overload is more heterogeneous. (Abb: RAAS = renin-angiotensin-aldosterone system; RNL = renalase.)



Medical Therapy	SAVR	TAVR
		
<ul style="list-style-type: none"> <li>- No evidence of sex-related differences in AS progression with medical therapy.</li> </ul>	<ul style="list-style-type: none"> <li>- Anemia/bleeding/blood transfusion.</li> <li>- Stroke events.</li> <li>- Renal Failure.</li> <li>- Heart Failure.</li> <li>- Postoperative stay.</li> <li>- Prosthesis-patient mismatch</li> <li>- In-hospital and 30-day mortality.</li> </ul>	<ul style="list-style-type: none"> <li>- Valve sizes.</li> <li>- Transfemoral approach.</li> <li>- Paravalvular regurgitation.</li> <li>- Prosthesis-patient mismatch .</li> </ul>
		<ul style="list-style-type: none"> <li>- Vascular/bleeding complications.</li> <li>- Long-term survival.</li> </ul>
		<ul style="list-style-type: none"> <li>- In-hospital and 30-day mortality.</li> </ul>

**Fig. 5.** Treatment options in severe aortic stenosis and women specific characteristics. (Abb.: SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; AS = aortic stenosis.)



**Central illustration.**

Illustrative representation of sex-related differences in aortic stenosis.

(Abb.: AVC = aortic valve calcification; AS = aortic stenosis; RV = right ventricle; LV = left ventricle; LGE = late gadolinium enhancement; ECV = extra cellular volume; EDV = end diastolic volume; BMI=body mass index; HTN=hypertension; CAD=coronary artery disease; PAD=peripheral artery disease; SOB=shortness of breath; GFR = glomerular filtration rate.)

**Table 1**

Most relevant interventional trials in aortic stenosis.

<b>Trial</b>	<b>Risk</b>	<b>No. patients included</b>	<b>Median age (years)</b>	<b>Women included (%)</b>
Partner B [54]	High	358	83	54
Partner A [81]	High	694	83	43
Core Valve U.S Pivotal High Risk [82]	High	795	83	47
Partner 2 [83]	Intermediate	1032	81	46
SURTAVI [84]	Intermediate	660	79	43
Partner 3 [85]	Low	950	73	33
Notion [86]	Low	280	79	47
Evolut Low Risk [87]	Low	1403	74	36

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**Table 2**

## Sex-specific critical knowledge gaps.

- 
- Future research in CMR, genetic factors, and other mechanisms proposed for sex-related differences in the pathophysiology of ACV, LV remodeling, LV hypertrophy and fibrosis.
  - Development of sex-specific AS preventive treatment targets, based on a better understanding of the pathophysiology in men and women.
  - Early implementation of prevention treatments with newer drugs targeting fibrotic pathways in women and anti-calcifying drugs in men.
  - Need of sex specific thresholds to improve AS diagnosis in women.
  - Future studies to analyze the importance of LV concentric hypertrophy and fibrosis on LGE CMR for risk stratification in women with asymptomatic severe AS, in order to decide a closer follow up and recommend AVR.
  - Further investigations to review the current thresholds to define low LVEF and LV dysfunction in women with AS, that would change clinical decision-making in treatment.
  - Studies can be retrospectively analyzed and future studies to determine whether earlier intervention in women, before maladaptive remodeling occurs, would be beneficial.
  - Determine if sex differences in vascular complications and bleeding after TAVR will persist with development of newer generation devices with smaller vascular footprints.
  - Impaired myocardial perfusion as a pharmacological therapeutic target in women with AS with persistent symptoms after AVR.
  - Prospective serial CMR anatomical, perfusion, and T1 imaging with serial inflammatory biomarkers analyzing sex-related differences are needed to understand mechanisms contributing to persistent symptoms and frequent hospitalization in patients after AVR.
  - Future studies with therapies targeting LV remodeling such as inhibitors of the renin-angiotensin-aldosterone.
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