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Sex-Related Factors in Valvular Heart Disease

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ABSTRACT

Numerous sex-based differences are observed across the spectrum of valvular heart disease, starting with pathophysiology and progression of disease, moving on to compensation and comorbidities (both cardiovascular such as coronary artery disease and noncardiovascular such as frailty), assessment of severity and hemodynamics including timing of intervention, and procedural risks/benefits and outcomes. The aortic valve is perhaps best understood with sex differences in both pathologic changes and response to volume and pressure overload, yet large gaps in our understanding still exist. Studies of other valve diseases have focused on differences in prevalence, presentation, and outcomes for surgical or transcatheter therapies. Defining sex-specific responses to valvular heart disease may improve disease recognition, define treatment strategies, and improve outcomes. (J Am Coll Cardiol 2022;79:1506–1518) © 2022 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Major differences between males and females exist in epidemiology, manifestation, pathophysiology, treatment, and outcome of cardiovascular diseases, such as coronary artery disease, pulmonary and systemic hypertension, and heart failure (HF).[1] However sex differences in valvular heart disease are underappreciated and poorly understood, contributing to disparities in treatment. The following paper reviews the sex differences in valvular heart disease presentation and management. The current knowledge gaps and areas of future research in this field are discussed.

VALVULAR HEART DISEASE AND PREGNANCY

Women with significant valve disease who are pregnant should be monitored in a tertiary-care center with a dedicated heart valve team including maternal-fetal medicine obstetricians with expertise in the management of high-risk cardiac conditions during pregnancy. During pregnancy, plasma volume and cardiac output reach a maximum of 40% to 50% above baseline, with 75% of this increase by the end of the first trimester. The increase in stroke volume is dependent on an increase in atrial and ventricular diameters while ventricular function is preserved. In the setting of significant valvular disease, with or without ventricular dilatation or dysfunction, there are increases in both maternal and fetal complications related to reduced stroke volume and uteroplacental blood flow.[2] The risks to the mother and fetus during pregnancy are highly dependent on the type and severity of valve disease. To assess the maternal risk of cardiac

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HIGHLIGHTS

- Sex-related differences in valvular disease epidemiology and ventricular responses to pressure and volume overload lead to differences in disease prevalence and clinical manifestations.
- Sex-related differences in pathophysiology should be considered in managing patients with valvular heart disease.
- Sex-specific research is needed to enhance understanding of valvular heart disease and improve clinical outcomes.

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation
AS = aortic stenosis
AV = aortic valve
EF = ejection fraction
HF = heart failure
LV = left ventricular/ventricle
MR = mitral regurgitation
TAVI = transcatheter aortic valve implantation
TEER = transcatheter edge-to-edge repair
TR = tricuspid regurgitation

complications during pregnancy, clinicians should perform a comprehensive echocardiographic assessment of ventricular and valvular function, intrapulmonary pressures, and aortic diameters, as well as clinical parameters such as symptom status, exercise capacity, and arrhythmias. Recommendations for the diagnosis and management of asymptomatic and symptomatic patients with native valve disease before as well as during pregnancy have been extensively covered in the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (**Table 1, Figure 1**).[3]

In women of child-bearing age, the decision about prosthetic valve type must balance the hemodynamic performance and long-term durability of mechanical valves which require potentially teratogenic anticoagulation (dose-dependent), with the reduced durability of bioprosthetic valves. In a study of 800 pregnancies, vitamin K antagonist treatment was associated with the lowest risk of adverse maternal outcomes; whereas the use of low-molecular-weight heparin (LMWH) throughout pregnancy was associated with the lowest risk of adverse fetal outcomes.[4] Fetal risk was similar between women taking ≤5 mg warfarin daily and women treated with LMWH. Because maternal and fetal mortality and morbidity, and because the risk of major cardiac events during pregnancy is much higher with mechanical valves, women often decide on a bioprosthetic valve. However, given the higher rate of structural valve dysfunction in younger patients, pregnant patients with pre-existing prosthetic dysfunction or prosthesis-patient mismatch can experience HF symptoms and increased fetal mortality.[5] The ACC/AHA guidelines for management of prosthetic valves during pregnancy are shown in **Table 1**.[3]

SEX DIFFERENCES IN INFECTIVE ENDOCARDITIS

Men predominate in most case series of infective endocarditis with male-to-female ratios ranging from 3:2 to 9:1; however, reported outcomes appear to be worse in women possibly related to the underuse of valve surgery given the studies showing female sex is a predictor of medical (vs surgical) management.[6] A small study evaluating the possible microbiological sex-based differences found: 1) no significant difference in management strategies between sexes; 2) a trend toward more right-sided infective endocarditis in men; 3) a significantly greater incidence of coagulase-negative staphylococcus in men (15.0% vs 3.8%, $P = 0.011$); and 4) a significantly greater incidence of culture negative endocarditis in women (23.8% vs 8.7%, $P = 0.004$).[7] On multivariate analysis, in-hospital mortality was not significantly different between sexes; however, all-cause mortality was significantly higher in women (31.3% vs 16.8%, $P = 0.018$). The reasons for sex differences in infective endocarditis are unknown and deserve further study.

SEX DIFFERENCES IN AORTIC VALVE DISEASE

The aortic valve (AV) is the most commonly diseased valve in high-income countries, with a 2-fold greater incidence of aortic stenosis (AS) than aortic regurgitation (AR). AS prevalence increases with age and reaches up to 12.4% among the elderly with more males than females.[8] Despite the 3:1 predominance of males with AS in young patients driven by the prevalence of congenital bicuspid AV, the ratio tends to reverse in the older age group with AS possibly more common in older women with a bicuspid AV and AR more common in young men.[9-11]

AORTIC STENOSIS. Calcification and fibrosis are the major components of leaflet thickening and stiffening. Calcific AS has a complex pathophysiology that involves inflammation, lipid infiltration, extracellular matrix remodeling, and finally transdifferentiation of the valvular interstitial cells into osteoblast-like cells and calcium deposition.[12] For the same hemodynamic severity of AS, women present with less AV calcification than men, measured by histology as well as by computed tomography (**Figure 2**).[13] Thresholds of AV calcification

TABLE 1 Recommendations for Diagnosis and Management of Patients With Valvular Heart Disease and Pregnancy

COR	LOE	Recommendations
Initial management of women with VHD before and during pregnancy		
1	B-NR	1. Women with suspected valve disease who are considering pregnancy should undergo a clinical evaluation and TTE before pregnancy.
1	B-NR	2. Women with severe valve disease (stages C and D) who are considering pregnancy should undergo prepregnancy counseling by a cardiologist with expertise in managing women with VHD during pregnancy.
1	B-NR	3. Pregnant women with severe valve disease (stages C and D) should be monitored in a tertiary-care center with a dedicated heart valve team of cardiologists, surgeons, anesthesiologists, and maternal-fetal medicine obstetricians with expertise in the management of high-risk cardiac conditions during pregnancy.
2a	B-NR	4. In asymptomatic women with severe valve disease (stage C1) who are considering pregnancy, exercise testing is reasonable before pregnancy for risk assessment.
Medical therapy for women with VHD before and during pregnancy		
2a	C-LD	1. In pregnant women with VHD, beta-blocker medications are reasonable as required for heart rate control or treatment of arrhythmias.
2a	C-LD	2. In pregnant women with VHD and HF symptoms (stage D), diuretic medications are reasonable if needed for volume overload.
3: harm	B-NR	3. In pregnant women with VHD, ACE inhibitors and ARBs should not be given because of fetal risk.
Intervention for women with native VHD before and during pregnancy		
1	B-NR	1. In symptomatic women with severe VHD who are considering pregnancy, intervention before pregnancy is recommended on the basis of standard indications.
1	C-EO	2. In women who require a valve intervention before pregnancy, the choice of prosthetic valve should be based on a shared decision-making process that accounts for the patient's values and preferences, including discussion of the risks of mechanical valves during pregnancy and the reduced durability of bioprosthetic valves in young women.
2a	C-LD	3. In asymptomatic women with severe rheumatic MS (mitral valve area ≤1.5 cm^2, stage C1) who are considering pregnancy, PMBC at a comprehensive valve center is reasonable before pregnancy for those who have favorable valve morphology.
2a	B-NR	4. In women of childbearing age who require valve replacement, bioprosthetic valves are preferred over mechanical valves because of the increased maternal and fetal risks of mechanical heart valves in pregnancy.
2a	C-EO	5. In asymptomatic women with severe AS (aortic velocity ≥4.0 m/s or mean pressure gradient ≥40 mm Hg, stage C) who are considering pregnancy, valve intervention before pregnancy is reasonable.
2b	C-EO	6. In asymptomatic women with severe AS (aortic velocity ≥4.0 m/s or mean pressure gradient ≥40 mm Hg, stage C1) who are considering pregnancy, do not meet COR 1 criteria for intervention, and have a preconception evaluation confirming the absence of symptoms (including normal exercise stress testing and serum BNP measurements), medical management during pregnancy may be considered to avoid prosthetic valve replacement.
2b	C-EO	7. In asymptomatic women with severe MR (stage C1) and a valve suitable for repair who are considering pregnancy, valve repair before pregnancy at a comprehensive valve center may be considered but only after detailed discussion with the patient about the risks and benefits of the surgery and its effect on future pregnancies.
During-pregnancy intervention		
2a	B-NR	1. In pregnant women with severe AS (mean pressure gradient ≥40 mm Hg, stage D), valve intervention during pregnancy is reasonable if there is hemodynamic deterioration or if there are NYHA functional class III or IV HF symptoms.
2a	B-NR	2. In pregnant women with severe rheumatic MS (mitral valve area ≤1.5 cm^2, stage D) and with valve morphology favorable for PMBC who remain symptomatic with NYHA functional class III or IV HF symptoms despite medical therapy, PMBC is reasonable during pregnancy if it is performed at a comprehensive valve center.
2a	C-LD	3. In pregnant women with severe valve regurgitation and with NYHA functional class IV HF symptoms (stage D) refractory to medical therapy, valve surgery is reasonable during pregnancy.
3: harm	C-LD	4. In pregnant women with VHD, valve surgeries should not be performed in the absence of severe HF symptoms refractory to medical therapy.
Prosthetic valves in pregnant women		
1	C-EO	1. Women with a prosthetic valve should undergo pre-pregnancy assessment, including echocardiography, by a cardiologist with expertise in managing women with VHD during pregnancy.
1	C-EO	2. Pregnant women with a mechanical prosthesis should be monitored in a tertiary-care center with a dedicated MDT of cardiologists, surgeons, anesthesiologists, and maternal-fetal medicine obstetricians with expertise in the management of high-risk cardiac conditions during pregnancy.
1	B-NR	3. Women with mechanical heart valves considering pregnancy should be counselled that pregnancy is high risk and that there is no anti-coagulation strategy that is consistently safe for the mother and baby.
1	B-NR	4. Pregnant women with a mechanical prosthetic valve who have prosthetic valve obstruction or experience an embolic event should undergo a TEE.

Continued on the next page

used to identify severe AS are sex-specific include 1,200 AU in women and 2,000 AU in men.[14] This difference in AV calcification remains significant after considering the smaller body, heart, and aorta size in women (severe AV calcification/aortic annulus area ≥300 AU/cm^2 in women and 500 AU/cm^2 in men).

Women present with more valvular fibrosis than men and denser connective tissue for a similar hemodynamic stenosis severity (**Figure 2**).[15] These sex differences in AS are probably explained by differences in the pathophysiological initiation and progression of AS, which are unfortunately far from being elucidated. Although hemodynamic progression of AS appears to be similar between men and women, the calcific progression is slower in women.[16] In stenosed bicuspid AV, fibrosis appears to predominate, especially in young women.[17]

TABLE 1 Continued

COR	LOE	Recommendations
Anticoagulation for pregnant women with mechanical prosthetic heart valves		
1	B-NR	1. Pregnant women with mechanical prostheses should receive therapeutic anticoagulation with frequent monitoring during pregnancy.
1	B-NR	2. Women with mechanical heart valves who cannot maintain therapeutic anticoagulation with frequent monitoring should be counseled against pregnancy.
1	B-NR	3. Women with mechanical heart valves and their providers should use shared decision-making to choose an anticoagulation strategy for pregnancy. Women should be informed that VKA during pregnancy is associated with the lowest likelihood of maternal complications but the highest likelihood of miscarriage, fetal death, and congenital abnormalities, particularly if taken during the first trimester and if the warfarin dose exceeds 5 mg/d.
1	C-LD	4. Pregnant women with mechanical valve prostheses who are on warfarin should switch to twice-daily LMWH (with a target anti-Xa level of 0.8 U/mL to 1.2 U/mL at 4 to 6 hours after dose) or intravenous UFH (with an aPTT 2 times control) at least 1 week before planned delivery.
1	C-LD	5. Pregnant women with mechanical valve prostheses who are on LMWH should switch to UFH (with an aPTT 2 times control) at least 36 hours before planned delivery.
1	C-LD	6. Pregnant women with valve prostheses should stop UFH at least 6 hours before planned vaginal delivery.
1	C-LD	7. If labor begins or urgent delivery is required in a woman therapeutically anticoagulated with a VKA, cesarean section should be performed after reversal of anticoagulation.
2a	B-NR	8. For pregnant women with mechanical prostheses who require a dose of warfarin ≤5 mg/d to maintain a therapeutic INR, continuation of warfarin for all 3 trimesters is reasonable after full discussion with the patient about risks and benefits.
2a	B-NR	9. For pregnant women with mechanical prostheses who require >5 mg/d of warfarin to achieve a therapeutic INR, dose-adjusted LMWH (with a target anti-Xa level of 0.8 to 1.2 U/mL at 4 to 6 hours after dose) at least 2 times per day during the first trimester, followed by warfarin during the second and third trimesters, is reasonable.
2a	B-NR	10. For pregnant women with mechanical prostheses who require a dose of warfarin >5 mg/d to achieve a therapeutic INR, and for whom dose-adjusted LMWH is unavailable, dose-adjusted continuous intravenous UFH during the first trimester (with aPTT 2 times control), followed by warfarin for the second and third trimesters, is reasonable.
2a	B-NR	11. For hemodynamically stable pregnant women with obstructive left-sided mechanical valve thrombosis, it is reasonable to manage with slow-infusion, low-dose fibrinolytic therapy.
2b	B-NR	12. For pregnant women with mechanical prostheses who require a warfarin dose >5 mg/d to achieve a therapeutic INR, dose-adjusted LMWH (with a target anti-Xa level of 0.8 to 1.2 U/mL at 4 to 6 hours after dose) at least 2 times per day for all 3 trimesters may be considered.
2b	B-NR	13. For pregnant women with mechanical prostheses who require a dose of warfarin ≤5 mg/d to maintain a therapeutic INR, dose-adjusted LMWH at least 2 times per day during the first trimester, followed by warfarin for the second and third trimesters, may be considered.
2b	B-NR	14. For pregnant women with mechanical prostheses, aspirin 75 to 100 mg daily may be considered, in addition to anticoagulation, if needed for other indications.
3: harm	B-NR	15. For pregnant women with mechanical prostheses, LMWH should not be administered unless anti-Xa levels are monitored 4 to 6 hours after administration and dose is adjusted according to levels.
3: harm	B-R	16. For patients with mechanical valve prostheses, anticoagulation with the direct thrombin inhibitor, dabigatran, should not be administered.
3: harm	C-EO	17. The use of anti-Xa direct oral anticoagulants with mechanical heart valves in pregnancy has not been assessed and is not recommended.

Reproduced with permission from Otto CM et al.[3]

ACE = angiotensin-converting enzyme; aPTT = activated partial thromboplastin time; ARB = angiotensin receptor blocker; AS = aortic stenosis; BNP = B-type natriuretic peptide; B-NR = level B-NR (nonrandomized); C-EO = level C-EO (expert opinion); C-LD = level C-LD (limited data); COR = class of recommendation; HF = heart failure; INR = international normalized ratio; LMWH = low-molecular-weight heparin; LOE = level of evidence; MDT = multidisciplinary team; MR = mitral regurgitation; MS = mitral stenosis; NYHA = New York Heart Association; PBMC = percutaneous balloon mitral commissurotomy; TEE = transesophageal echocardiography; TTE = transthoracic echocardiogram; UFH = unfractionated heparin; VHD = valvular heart disease; VKA = vitamin K antagonist.

The response to pressure overload created by the AS also exhibits sex differences: left ventricular (LV) remodeling with a concentric pattern is observed more frequently in women, with an eccentric pattern in men. This could be partly explained by the presence of greater diffuse fibrosis within the myocardium detected by extracellular volume fraction on cardiac magnetic resonance in women compared to men, despite similar degrees of pressure overload and prevalence of coronary artery disease.[16] In addition to greater fibrosis of the myocardium, differences in remodeling may also be related to a higher incidence of hypertension in women and poorly understood interactions with sex hormones. Concentric remodeling was identified as a predictor of worse outcome in women but not in men.[18] At presentation, women may have a smaller LV, preserved ejection fraction (EF), and lower stroke volume index leading to more paradoxical low flow AS (ie, stroke volume index ≤35 mL/m^2). However, the threshold to define low flow should also be sex specific, as the excess of mortality after AV intervention in men occurs at ≤40 mL/m^2.[19]

Long-term outcomes for AS also show significant differences between women and men. In 2 recent large retrospective studies, women were older at initial presentation, with fewer comorbidities and more symptoms.[20,21] Even after matching for baseline differences, women had a higher long-term mortality (inverse-propensity weighting hazard ratio: 1.91;

FIGURE 1 **Algorithm for Management of Pregnant Patients With Mechanical Prosthesis**

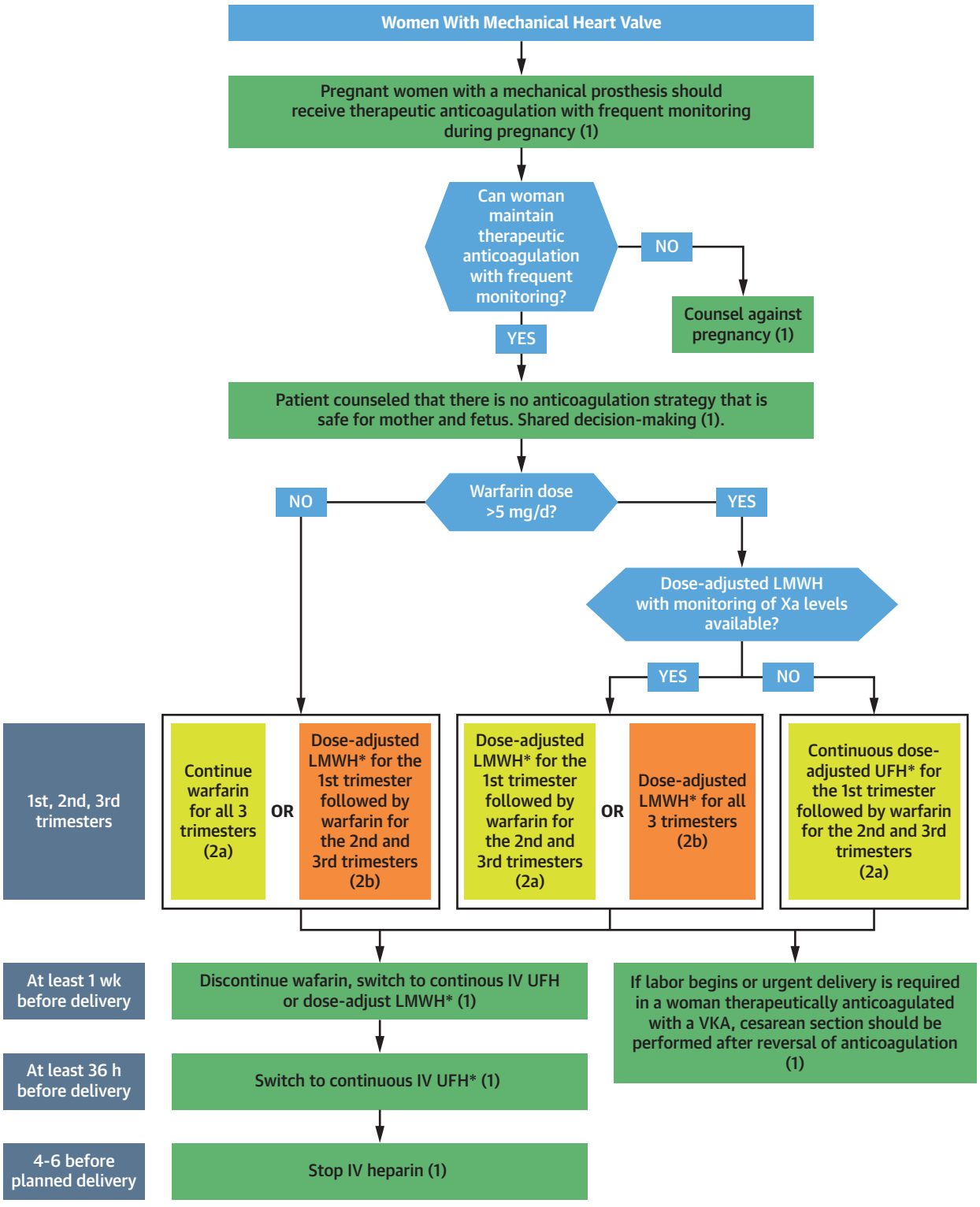

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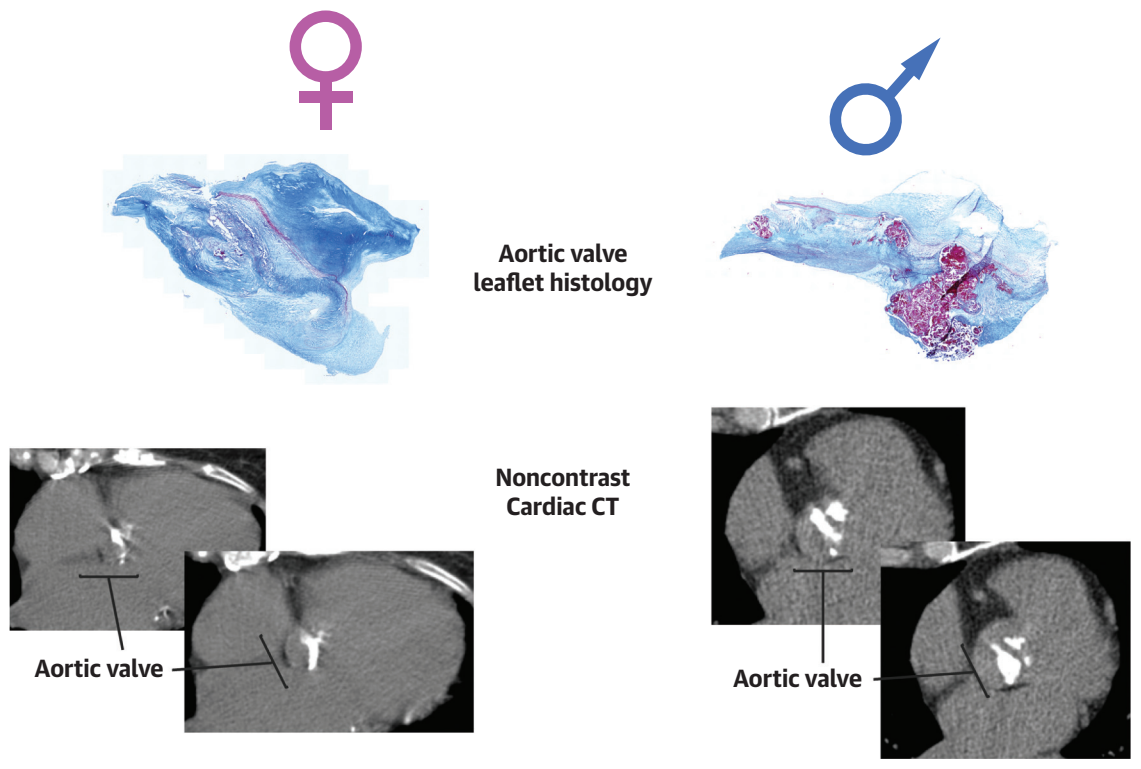
FIGURE 2 Stenosed Aortic Valve at Histology and Noncontrast Computed Tomography



(Top) Histologic examination of an aortic valve leaflet from a woman and a man were stained by trichrome Masson staining which reveals fibrosis in **blue** and calcification in **pink**. Calcific deposition is more prominent in the leaflet from a male. **(Bottom)** Using computed tomography, calcification should be measured on the native axial noncontrast scan reconstructed with 3 mm thickness and 1.5 mm spacing. The aortic valve is generally visible on 4-8 slices (2 slices shown here). Calcium (**white** on CT) is more abundant in the male scan compared to the female scan, despite both having hemodynamically severe aortic stenosis.

95% CI: 1.14-3.22; $P = 0.01$),[21] than men despite their longer life expectancy in the general population. In addition, men more frequent underwent early AV replacement (OR: 1.49; 95% CI: 1.18-1.97).[20]

AORTIC REGURGITATION. The etiologies of chronic AR include bicuspid valve, myxomatous degeneration, aorta dilation, and inflammatory syndromes. Aortic dilatation in bicuspid AV is observed more frequently in men; however, this does not appear to affect outcomes adversely, possibly related to the relative infrequency of vascular complications such as aortic dissection.[22] However, women exhibited a significantly higher relative risk of death in the tertiary-referral centers (~40% higher) and AV replacement cohorts (~20% higher), which was independently associated with AR in women.[11] This may be related to the guideline-recommended absolute end-systolic diameter cutoffs for intervention, which may favor earlier referral for men compared to women. Recent cardiac magnetic resonance studies

FIGURE 1 Continued

Pregnant women taking vitamin K antagonists (VKAs) are at increased risk of both serious maternal complications and poor fetal outcomes. However, women with mechanical heart valves require uninterrupted therapeutic anticoagulation throughout pregnancy. The 3 potential strategies outlined by current guidelines are shown here: 1) Continue warfarin throughout pregnancy; 2) use heparin throughout pregnancy; and 3) use sequential therapy, with heparin during the first trimester and warfarin during the second and third trimesters. Reproduced with permission from Otto et al.[3] *Dose-adjusted LMWH should be given at least 2 times per day, with close monitoring of anti-Xa levels. Target to Xa level of 0.8-1.2 U/mL, 4-6 hours after dose. Trough levels may aid in maintaining patient in therapeutic range. Continuous UFH should be adjusted to an activated partial thromboplastin time (aPTT) 2 times control. Note: the numbers in the parenthesis indicate the level of recommendation. IV = intravenous; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

TABLE 2 Data Evaluating Outcomes of TAVI by Sex

	Device Success	Post-TAVI AR ≥2+	Permanent Pacemaker	Major Vascular Complication	Life-Threatening or Major Bleeding	Stroke @30 d	All-Cause Mortality @30 d	All-Cause Mortality @1 y
TVT Registry (2016)[46] (N = 23,652)								
F = 50 M = 50	F: 92.6 M: 92.5	NA	F: 8.9 M: 8.5	**F: 8.3** **M: 4.4**	F: 8.01 M: 5.96	F: 2.58 M: 1.86	F: 5.6 M: 4.28	**F: 21.3** **M: 24.5**
P value or aHR (95% CI)	0.51	NA	1.08 (0.88-1.32)	**1.7 (1.34-2.14)**	1.19 (0.99-1.44)	NS	0.89 (0.71-1.11)	**0.73 (0.63-0.85)**
CENTER Registry (2019)[48] (N = 23,652)								
F = 58 M = 42	NA	NA	**F: 12.2** **M: 16.7**	NA	**F: 6.7** **M: 4.4**	F: 2.3 M: 2.5	F: 5.9 M: 5.5	NA
RR (95% CI)	NA	NA	**0.7 (0.7-0.8)**	NA	**1.5 (1.3-1.8)**	0.9 (0.7-1.2)	1.1 (1.0-1.3)	NA
O'Connor et al Meta-analysis (2015)[47] (N = 11,310)								
F = 49 M = 51	F: 97.3 M: 96.9	**F: 19.4** **M: 24.5**	**F: 11.9** **M: 15.3**	**F: 6.3** **M: 3.4**	**F: 10.5** **M: 8.5**	**F: 4.4** **M: 3.6**	F: 6.5 M: 6.5	**F: 17.3** **M: 21.8**
P value or aHR (95% CI)	0.22	**<0.001**	**<0.001**	**<0.001**	**0.003**	**0.029**	0.93	**0.79 (0.73-0.86)**

Values are % unless otherwise indicated. **Bold** indicates statistically significant differences.

aHR = adjusted hazard ratio; AR = aortic regurgitation; CENTER = Cerebrovascular Events in Patients Undergoing Transcatheter Aortic Valve Implantation With Balloon-Expandable Valves Versus Self-Expandable Valves; CI = confidence interval; F = female; M = male; RR = relative risk; NA = not available; NS = not significant; TAVI = transcatheter aortic valve implantation; TVT = transcatheter valve therapy.

suggest that in patients with chronic AR (with or without bicuspid morphology), LV dilatation is closely associated with AR regurgitant fraction in men but not in women.[23] LV volumes indexed to body size were normal in 35.3% of women vs 8.7% men ($P < 0.001$); however, on comprehensively adjusted Cox regression model, women were at significantly higher risk for the composite endpoint of HF hospitalization, unscheduled AR intervention, and cardiovascular death when compared to men (adjusted hazard ratio [HR]: 1.81; 95% CI: 1.09-3.03; $P = 0.022$).

In asymptomatic patients, current guidelines give a Class 2a recommendation for intervening on severe AR if the LV is severely enlarged (LV end-systolic dimension index >25 mm/m^2), and a Class 2b recommendation if there is progressive increase in LV dilatation (LV end-diastolic dimension >65 mm)[3]; however, given the body size and sex-based differences in LV response to AR, these numbers may not be appropriate for females. A recent study of ≥ moderate-to-severe chronic AR showed increased mortality with a lower LV end-systolic dimension index of 20 to 25 mm/m^2 (HR: 1.53; 95% CI: 1.01-2.31); however, 82% of patients in this study were men, again raising significant questions about defining the appropriate sex-based cutoff points for intervention.[24]

SEX DIFFERENCES IN MITRAL REGURGITATION

Mitral regurgitation (MR) is frequent and associated with significant morbidity and mortality.[3] The majority of patients with severe primary as well as secondary MR remain untreated, with a higher proportion of females among untreated patients.

PRIMARY MR. The most common cause of chronic primary MR in Europe and the United States is mitral valve prolapse with a trend towards higher prevalence of mitral valve prolapse among women.[25] In a retrospective analysis of more than 8,000 individuals with mitral valve prolapse, LV and atrial diameters were larger in females after normalization to body surface area, highlighting the need for sex-specific or indexed criteria for intervention.[26] Arrhythmogenic mitral valve prolapse, more common in young adult women, accompanied by morphofunctional abnormalities of the mitral annulus (ie, mitral annular disjunction and systolic curling) is associated with fibrosis of the papillary muscles and inferobasal LV, which may be the substrate for sudden cardiac death even in the absence of significant MR.[27] The role of genetic mutations associated with mitral valve prolapse and reasons for higher disease prevalence in women is unknown.

SECONDARY MR. Secondary MR develops in individuals with LV remodeling on the basis of ischemic or nonischemic etiologies (ie, ventricular function MR) as well as left atrial and annular remodeling (ie, atrial functional MR).[3] Among 28,820 participants from 4 community-based cohorts followed for incident HF over 12 years, men had an almost 2-fold higher risk than women for HF with reduced EF, although HF with preserved EF accounts for a higher proportion of incident HF in women compared to men.[28] This was confirmed in the Swedish HF Registry of 42,987 patients in which only 29% of females had reduced EF, 39% had mid-range EF, but 55% had

preserved EF.[29] Thus, it is not surprising that females represented only 36% of patients in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial and 25% of patients in the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial.[30,31]

NONRHEUMATIC CALCIFIC MITRAL STENOSIS. Mitral annulus calcification with extension onto the leaflets and chordae may result in both narrowing of the annulus and restriction of leaflet mobility leading to nonrheumatic mitral stenosis, a condition with a 5-year mortality rate of more than 50%, irrespective of sex.[32] Female sex is a predictor of incident mitral annulus calcification, and 68.1% of patients in the transcatheter mitral valve replacement in Mitral Annulus Calcification Global Registry were female.[33,34]

RHEUMATIC MITRAL STENOSIS. Rheumatic heart disease patients are most often young, predominantly female, and have a high prevalence of major cardiovascular complications with far-reaching downstream effects on reproductive health and access to care.[35] Although women experience favorable outcomes compared with men when treated by percutaneous balloon valvuloplasty, access to these procedures is low in low-income countries.[36]

SEX DIFFERENCES IN TRICUSPID VALVE DISEASE

There is a strong association with female sex and prevalence of significant tricuspid regurgitation (TR) such that by the 8th decade, women with TR outnumber their male counterparts by 4:1.[37] Thus, a greater number of females tend to undergo isolated tricuspid valve (TV) surgery with no sex-related differences in 30-day or 5-year mortality.[38] Similarly, most participants in transcatheter TV device early feasibility trials are female.

Two recent studies have evaluated the sex differences in etiology, comorbidities, echocardiographic parameters, and prognosis in patients with significant TR.[39,40] Gual-Capllonch et al[39] studied 251 consecutive patients with functional TR and found that compared to males, females tended to have a higher prevalence of significant functional TR, which presented at an older age with more atrial function disease given the more frequent history of arterial hypertension, higher E/e' ratio, and higher LV ejection fraction. In fact, atrial fibrillation predicted TR in females but not in males. Dietz et al[40] studied 798 (51%) females and 771 (49%) males and confirmed that females were diagnosed with significant TR at an older age and the etiology was more often left valvular disease and atriogenic functional TR. In the total population, females had better 10-year survival rates compared with males (49% vs 39%; $P = 0.001$); however, after propensity score matching, there was no significant difference in mortality ($P = 0.228$). The TR etiologies determined outcomes; patients with TR related to left valvular disease (more likely female) or LV dysfunction (more likely male) had higher all-cause mortality compared with primary TR.

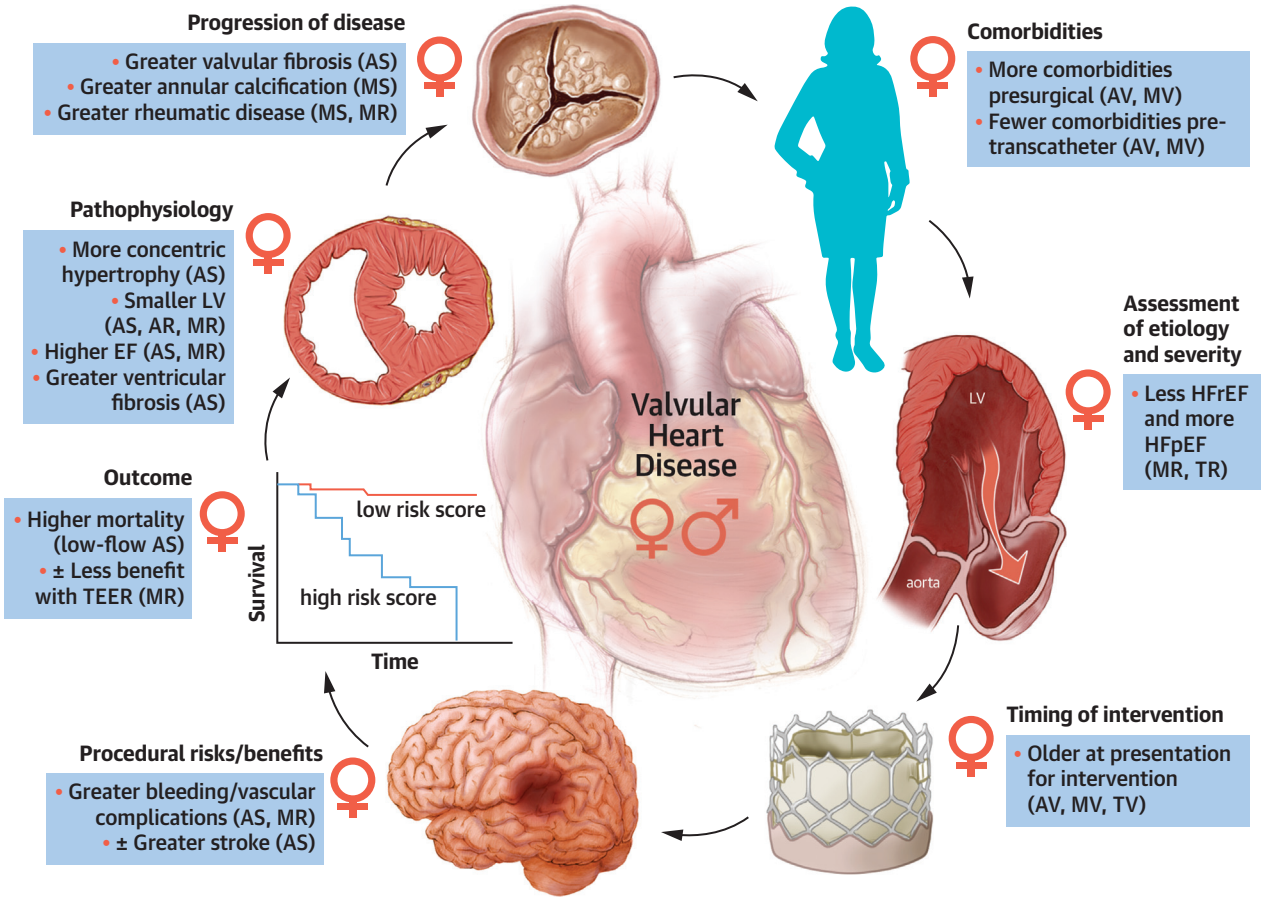
SEX DIFFERENCES IN OUTCOMES AND ACCESS FOR VALVE SURGERY

The influence of sex on outcomes after valve surgery is controversial. Older series and registry data have suggested worse outcomes for women, but closer analysis suggests outcomes are most related to disease/comorbid state at time of surgery. However, women are less frequently referred for surgery after a diagnosis of significant disease.

AV SURGERY. Mortality from AV surgery in the United States has been gradually decreasing, with the larger gender gap seen 35 years ago, narrowing to minimal in the last decade. A study of 166,809 patients (only 37% female) who underwent AV replacement showed women are typically older, and had more nonatherosclerotic comorbidities than men at presentation.[41] In the propensity-matched groups, vascular complications and blood transfusion were higher in women, and in-hospital mortality remained slightly higher in women (3.3% vs 2.9%; $P < 0.001$) even after adjusting for age and other confounders. Andrei et al[42] studied 628 consecutive patients (only 24% female) with bicuspid AV who underwent AV surgery and found that women presented with more advanced age and increased comorbidities resulting in higher in-hospital mortality risk scores. After propensity score matching, women received more postoperative blood products and had more prolonged postoperative lengths of stay. However, operative, discharge, and 30-day mortality and overall survival were not significantly different.

MITRAL VALVE SURGERY. Similarly, women are typically older and with more comorbidities and higher symptomatology than men at presentation for mitral valve surgery.[43,44] However, after propensity matching (including for age, symptoms, type of mitral disease, comorbidities, and ventricular function), outcomes between men and women were not

CENTRAL ILLUSTRATION **Sex-Related Differences in Valvular Heart Disease**



Hahn RT, et al. J Am Coll Cardiol. 2022;79(15):1506–1518.

Sex-related differences in valvular heart disease involve differences in disease pathophysiology, progression, comorbidities, assessment of severity and hemodynamics, timing of intervention, procedural risks/benefits and overall outcomes. AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; EF = ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; MR = mitral regurgitation; MS = mitral stenosis; MV = mitral valve; TEER = transcatheter edge-to-edge repair; TR = tricuspid regurgitation; TV = tricuspid valve.

significantly different, suggesting that the sex differences in unmatched studies are related to late presentation and comorbidities. Women comprised <50% of the surgical cohort in these studies and <30% of patients treated with minimally invasive techniques.[45]

Interestingly, Kandula et al[44] also showed that women referred for surgery who appeared to be at similar disease stages to men had more subclinical ventricular dysfunction by echocardiographic speckle-tracking echocardiography. Greater use of speckle-tracking echocardiography may allow earlier detection of mitral disease progression and earlier surgical referral.

SEX DIFFERENCES IN TRANSCATHETER VALVE INTERVENTIONS

The use of transcatheter aortic valve implantation (TAVI) for AS and transcatheter edge-to-edge repair (TEER) for MR are now accepted treatment options in specific patient populations.[3] Randomized trials and registry data in both of these areas has provided insight into the sex differences for these treatment options.

TRANSCATHETER AORTIC VALVE IMPLANTATION. TAVI is the standard of care for patients with symptomatic severe AS at high and prohibitive risk for surgical intervention. In addition, current guidelines

give TAVI a Class I indication for patients aged 65 to 80 years with characteristics suitable for transfemoral approach.[3] Females constitute almost one-half of the patients studied in trials and tend to be older with fewer comorbidities (**Table 2**).[46,47] Procedural outcomes of TAVI by sex show no differences in device success; however, female sex is associated with an increased rate of major vascular complications and major bleeding.[46-48] The lower incidence of ≥ moderate paravalvular regurgitation may offset the negative mortality impact of these complications because multiple single- and multicenter studies, as well as meta-analyses, have shown better mid-term and long-term survival among women undergoing TAVI compared to men, consistent with their lower baseline risk profile and longer mean life expectancy.[49,50]

This survival advantage may not extend to all patient populations. In the TOPAS (Multicenter Prospective Study of Low-Flow Low-Gradient Aortic Stenosis) study, women had similar outcomes to men in the medically managed subset, but markedly higher mortality in the subset of patients undergoing AV intervention (HR: 1.82; 95% CI: 1.08-3.13; $P = 0.0248$).[51] This sex-specific disparity in long-term survival in patients with low flow may be related to the previously discussed differential myocardial structural damage due to pressure overload.

In contradistinction to these prior studies, recent analysis of the high- and intermediate-risk patients in the PARTNER SAPIEN 3 (Placement of Aortic Transcatheter Valves) study as well as the CENTER (Cerebrovascular Events in Patients Undergoing Transcatheter Aortic Valve Implantation With Balloon-Expandable Valves Versus Self-Expandable Valves) collaboration showed no apparent sex-specific differences in survival or stroke on multivariable analysis, possibly reflecting the changing demographic of patients enrolled, use of newer-generation valves and delivery systems, and more accurate valve sizing techniques.[48,52]

TEER FOR MR. Multiple TEER registries have consistently found that, compared to men, women undergoing TEER are older with fewer comorbidities and less LV dilatation.[53,54] Procedural success and MR reduction are similar between sexes with no differences in mortality or rehospitalization rates. However, studies differ with regard to clinical improvement. At 1-year follow-up, the TRAMI (Transcatheter Mitral Valve Interventions) registry showed that women had less improvement in New York Heart Association functional class despite lower reintervention rates.[53] The EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation) study showed equivalent quality of life and symptomatic improvements in females and males.[54] Finally, the subgroup analysis of the randomized COAPT trial suggested that improved outcomes with TEER may be attenuated in females (HR: 0.77; 95% CI: 0.49-1.21) compared to males (HR: 0.44; 95% CI: 0.3-0.61).[30] Clearly, data regarding sex differences in outcomes after TEER require further study.

IMPLICATIONS FOR CLINICAL CARDIOLOGY PRACTICE AND RESEARCH

As delineated above, the spectrum of valvular heart disease manifests and is managed differently in men and women (**Central Illustration**). Observational studies have helped define these differences, but there are limited studies elucidating the genetic, hormonal, or pathophysiologic causes. Multiple sex differences in valvular heart disease stand out, including disease severity metrics such as aortic calcification (ie, in women, more fibrosis of the AV, more calcification of the mitral annulus), ventricular remodeling (ie, concentric remodeling with AS, higher EF with MR), delayed presentation in women for all valve diseases, and differences in guideline-recommended intervention. These differences may be compounded rather than resolved by commonly used allometric indexes for indexing such as using body surface area, as this assumes that women are simply smaller men and does not capture significant differences in pathophysiology with implications for timing of interventions, and eventually outcomes. For example, in AR, sex-based differences in the relationship between LV dilatation and regurgitant fraction mean that relying on LV volumes indexed to body size to judge the timing of intervention results in delayed surgery in women and much worse outcomes.[23] Collectively, this argues strongly for more research specific to sex/gender in aortic, mitral, and tricuspid disease and greater physician and patient awareness of sex differences in valvular disease pathophysiology and presentation. Sex-specific research on valvular heart disease pathophysiology is needed to clarify each of these areas separately for men and women to improve delivery of care and outcomes.

In addition to sex-specific research, defining individual pathophysiology rather than population-based

descriptions may help to bypass the problem of small numbers of women in trials and historical difficulties in extrapolating results of studies in men to the assessment of women. Advanced imaging can be used to create a personalized or precision picture of cardiovascular status, which is quantitative and sensitive, and unique to each individual. Mechanistic studies such as those evaluating myocardial function by global longitudinal strain measurement are highly promising. Recent studies showing greater strain impairment in women compared to men undergoing mitral valve repair suggest persistent delays in intervention in women, with a strong correlation between impaired strain and significant adverse outcomes.[44] Similar data exist showing that strain is useful for risk stratification in AS, but sex/gender-specific thresholds for decision making are not yet defined or validated.

Much has been written about the need to collect, analyze, and report data regarding sex and gender in cardiovascular disease, including valvular heart disease. Investigators, funding agencies, industry, U.S. Food and Drug Administration, journals, and other members of the scientific enterprise must prioritize such research and analyses, and not accept as final any datasets with too few women for independent analysis. Strategies to increase the diversity of clinical trial populations are increasingly embraced but will take time to improve representation in the literature. In this respect, the recent decision by *JACC: Heart Failure* to include "diversity of authorship and leadership among our considerations for potential publication" is a significant step forward as trials led by women often have more diverse cohorts.[55]

A significant barrier to fully understanding the impact of sex/gender on valvular heart disease is the historic assumption that complex biologic differences can be rigorously defined when group membership is based on gender presentation alone. Even use of sex at birth may not be sufficient. Accurate group assignment is essential for sex/gender-specific science.

CONCLUSIONS

Sex differences in valvular disease epidemiology as well as valvular and ventricular response to pressure and volume overload result in differences in disease prevalence and manifestation. These differences may result in sex/gender differences in presentation and treatment that could affect outcomes. Sex-specific research is needed to fully understand each of these areas separately for men and women.

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Dr Hahn has received speaker fees from Abbott Structural, Edwards Lifesciences, and Philips Healthcare; has received consulting fees from Abbott Structural, Boston Scientific, Edwards Lifesciences, and Gore & Associates; has equity with Navigate; and is Chief Scientific Officer for the Echocardiography Core Laboratory at the Cardiovascular Research Foundation for multiple industry-sponsored trials, for which she receives no direct industry compensation. Dr Clavel has received core lab contracts with Edwards Lifesciences; and has received research grants from Medtronic. Dr Mascherbauer has received speaker fees from Abbott Vascular, Boston Scientific, and Edwards Lifesciences; has received proctoring fees from Abbott Vascular and Edwards Lifescience; and is on advisory boards for Boston Scientific and Shockwave. Dr Mick has received consulting fees from Medtronic, Johnson & Johnson, and Cryolife. Dr Asgar has received consulting fees from Medtronic, Edwards Lifesciences, and Abbott; and has received research funding from Abbott Vascular. Dr Douglas has reported that she has no relationships relevant to the contents of this paper to disclose.

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