News in February 2024

1. Addressing HF in Latin American Women: A Call For Action

Heart failure (HF) and cardiovascular disease have reached epidemic levels in Latin American (LATAM), with rising age-standardized mortality rates, and the disparities seen in women worldwide in terms of diagnosis and treatment are also relevant when it comes to HF in LATAM women. Collaboration between health care systems, professional organizations, governmental entities, among others, is needed to reduce these inequalities, according to an article published Jan. 8 in the Journal of Cardiac Failure.

Cesar J. Herrera, MD, FACC**,** et al., write in their call to action that HF in low-and-middle-income countries, and especially among LATAM women, is a rarely addressed topic in the scientific community. Some 335 million women live in the 33 countries comprising LATAM.

The authors write that some features of HF in women in LATAM include a generally younger population, a strong influence of reproductive risk factors, a high prevalence of rheumatic heart disease, Chagas cardiomyopathy and untreated congenital heart disease, and possibly more HFrEF than HFpEF, but that more research is needed to fully characterize it. Among relevant social determinants of health are rural residence and related limitations in transportation; racial, cultural and religious beliefs; and lower health expenditure than in developed nations. In addition, women in LATAM "constitute an essential axis in family structures as caretakers and providers of financial support, a fact that, unfortunately, has been linked to lower rates of preventive care use and delays in medical attention."

"In summary, the urgent need to address HF in LATAM expands beyond the understanding of how social determinants of health impact the well-being of women; it should also embrace specific aspects of HF potentially unique to the region, including the influence of genetics, specific etiologies and clinical expressions," they write.

2. Novel Score to Predict LV Recovery in Peripartum Cardiomyopathy

Study Questions:

Can a clinical tool to predict left ventricular (LV) recovery at 6 months among individuals with peripartum cardiomyopathy (PPCM) be established?

Methods:

Data from the European Society of Cardiology (ESC) EURObservational Research Programme (EORP) registry were collected from 2012–2018 in 51 countries. The PPCM registry included 752 women meeting diagnostic criteria for PPCM. LV recovery was defined as ejection fraction (EF) ≥50% at 6 months. Statistical modeling used data from the registry participants and then an integer score was created.

Results:

Of 465 individuals with an echocardiogram performed at 6 months, 46.5% recovered. The variables included were: 1) baseline LVEF, 2) baseline LV end-diastolic diameter, 3) human development index (related to the country's development status), 4) duration of symptoms, 5) QRS duration, and 6) pre-eclampsia. The C-statistic of this model was 0.79 (95% confidence interval [CI], 0.74-0.83).

Conclusions:

The ESC EORP PPCM Recovery Score can be applied to predict LV recovery at 6 months in individuals with PPCM.

Perspective:

PPCM is a devastating diagnosis and associated with highly variable outcomes, from full recovery to heart transplantation or death. Previously, the most reliable predictor of recovery was the baseline EF. In this study, a clinical prediction tool using six variables is established. In this cohort, patients are

more likely to recovery if they had a higher baseline EF, smaller LV diameter, narrow QRS, shorter duration of symptoms, pre-eclampsia, and live in a country with higher social and economic development. While several of these individual variables have previously been associated with LV recovery, this is the first clinical tool that combines them into a model that predicts recovery.

3. Cardio-Obstetrics Team-Based Management of a Pregnant Patient With Severe Bioprosthetic Aortic Valve Disease

Abstract

A 38-year-old pregnant patient was managed by the cardio-obstetrics multidisciplinary team for severe degenerative bioprosthetic aortic valve failure. She was medically managed utilizing echocardiogram and brain natriuretic peptide until she demonstrated worsening heart failure. A valve and cardio-obstetrics team evaluation led to valve-in-valve transcatheter aortic valve replacement at 30 weeks' gestation.

Case Presentation

The patient was a 38-year-old G1P000 woman with bicuspid aortic valve disease who 5 years prior to presentation underwent surgery for mixed aortic valvular disease and ascending aortic dilation of 5.2 cm. She received a #23 St. Jude Medical Trifecta stented bioprosthetic graft with end-to-end anastomosis 8-mm Terumo Gelweave Dacron graft. Four years after her surgery, she had issues with swelling and dyspnea. Transthoracic echocardiography (TTE) demonstrated normal left ventricular ejection fraction (LVEF), with a mean gradient across her bioprosthetic aortic valve replacement (AVR) of 22 mm Hg. A year later, she was diagnosed with first-trimester pregnancy. TTE at that time demonstrated an LVEF of 65% and a mean AVR gradient of 33 mm Hg. She was referred to a cardio-obstetrics program at 16 weeks' gestation. TTE demonstrated an LVEF of 70% and mean AVR gradient of 46 mm Hg, with a dimensionless index of 0.28 consistent with moderate-severe stenosis (**Figures 1** and **2**, **Videos 1** and **2**). Her brain natriuretic peptide (BNP) was 106 pg/mL. She was doing well with no cardiac

symptoms. Due to her valvular disease and aortopathy, she was classified as modified World Health Organization classification (mWHO) III.

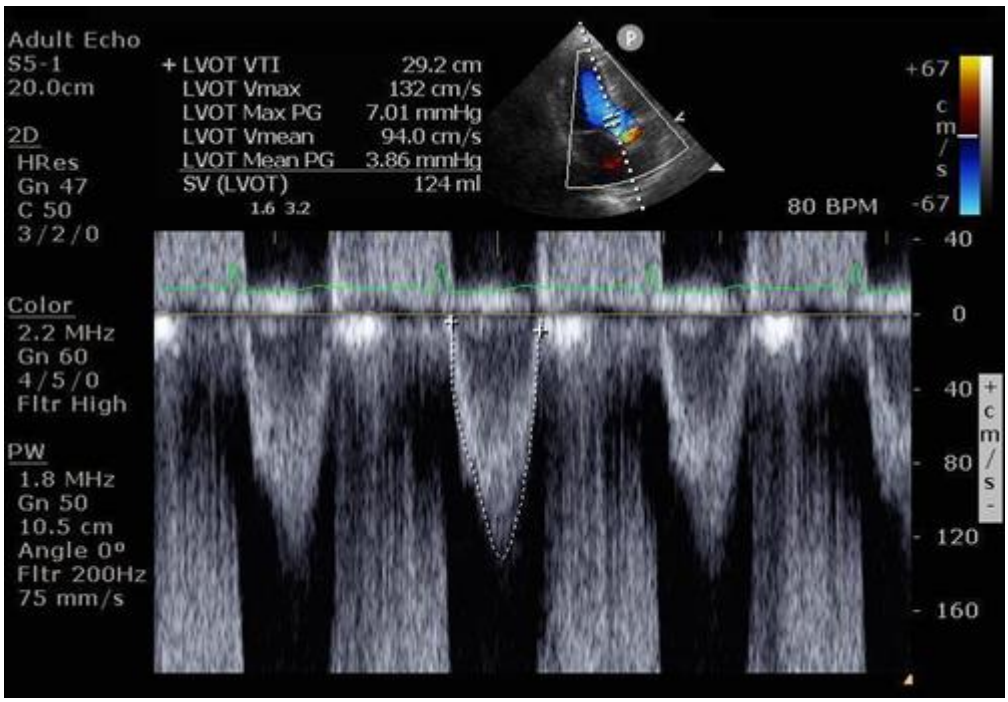


Figure 1

Spectral Doppler Bioprosthetic Aortic Valve Replacement LVOT VTI, Early Second Trimester

The left ventricular outflow tract (LVOT) velocity time integral (VTI) was 29, spectral Doppler aortic valve early second trimester. VTI was 105, dimensionless index was 0.28, and mean aortic valve replacement gradient was 46.4 mm Hg, indicating moderate stenosis. PG = pressure gradient; PW = pulsed wave Doppler; SV = stroke volume; Vmax = peak velocity; Vmean = mean velocity.

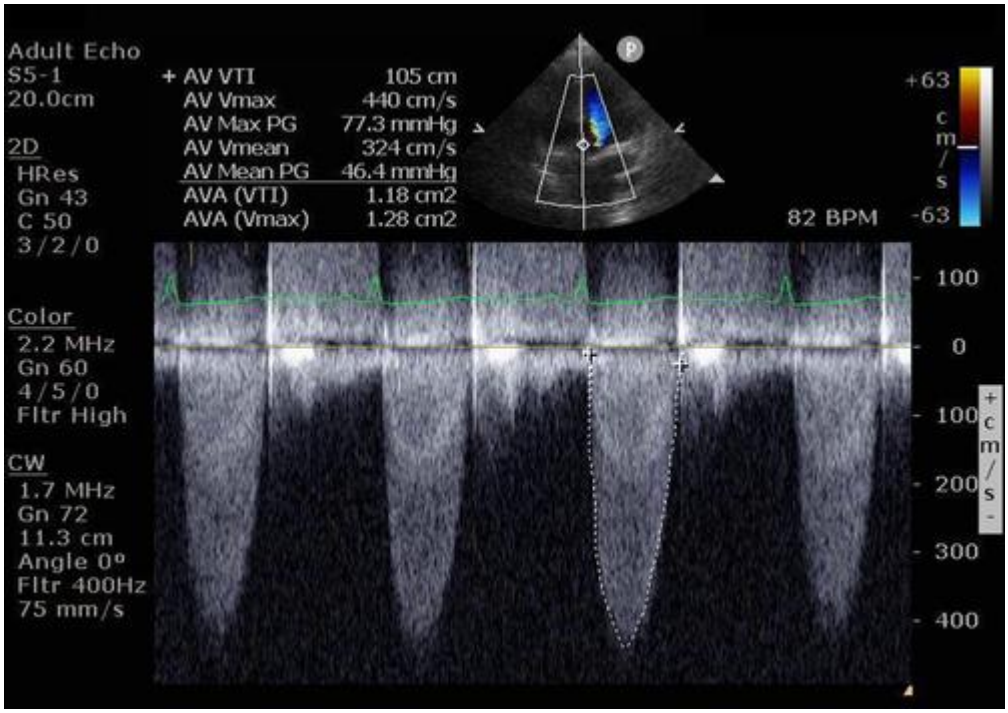


Figure 2

Spectral Doppler Bioprosthetic Aortic Valve Replacement Aortic VTI, Early Second Trimester

The LVOT VTI was 29, spectral Doppler Aortic valve early second trimester. VTI was 105, dimensionless index was 0.28, and mean aortic valve (AV) replacement gradient was 46.4 mm Hg, indicating moderate stenosis. AVA = aortic valve area; CW = continuous wave Doppler; other abbreviations as in **Figure 1**.

Learning Objectives

- To be able to demonstrate the benefit of multidisciplinary management of pregnant patients with cardiac valvular disease utilizing risk stratification, imaging, and cardiac biomarkers.
- To characterize the risk associated with valvular disease in pregnancy and identify patients for whom intervention may improve perinatal outcomes.

She started to have mild heart failure symptoms in her second trimester but was managed with low-dose oral furosemide and monthly TTE as an outpatient. TTE mid second trimester had an ejection fraction of 73%, mean AVR gradient of 67 mm Hg, moderate-to-severe aortic regurgitation, and pressure half time 148 ms (**Figures 3** and **4**, **Video 3**). Due to increasing symptoms and near severe aortic regurgitation, valve team evaluation was undertaken. Transcatheter aortic valve replacement (TAVR) computed tomography (CT) to evaluate for valve-in-valve TAVR was completed. The CT scan demonstrated degeneration of the AVR leading to incomplete closure as the cause of her stenosis and regurgitation. The valve and cardio-obstetrics program teams deemed her suitable to proceed with valve-in-valve TAVR if worsening heart failure refractory to medical management (**Figure 5**, **Video 4**). Monthly evaluation for ongoing severe AVR stenosis and regurgitation was performed. Early in the third trimester, her BNP increased from 200 to 459 pg/mL, and she had worsening lower extremity edema leading to increase in furosemide.

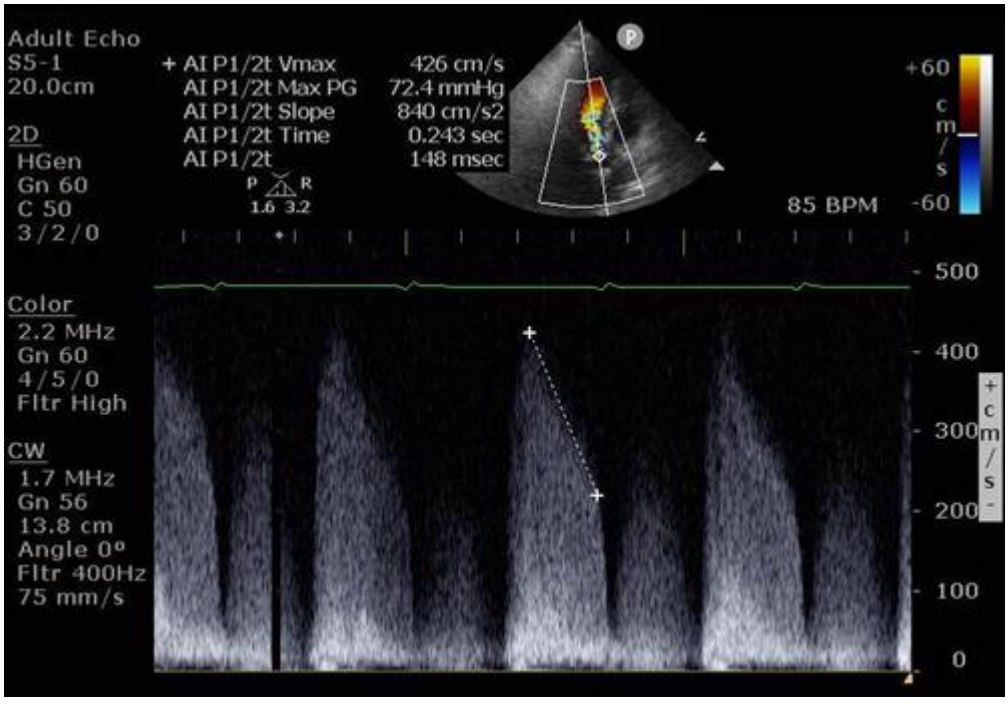


Figure 3

Spectral Doppler Bioprosthetic AV Replacement Aortic Regurgitation, Late Second Trimester

Pressure half time was 148 ms, mean AV replacement gradient was 67 mm Hg, and there was severe stenosis and regurgitation. Abbreviations as in **Figures 1** and **2**.

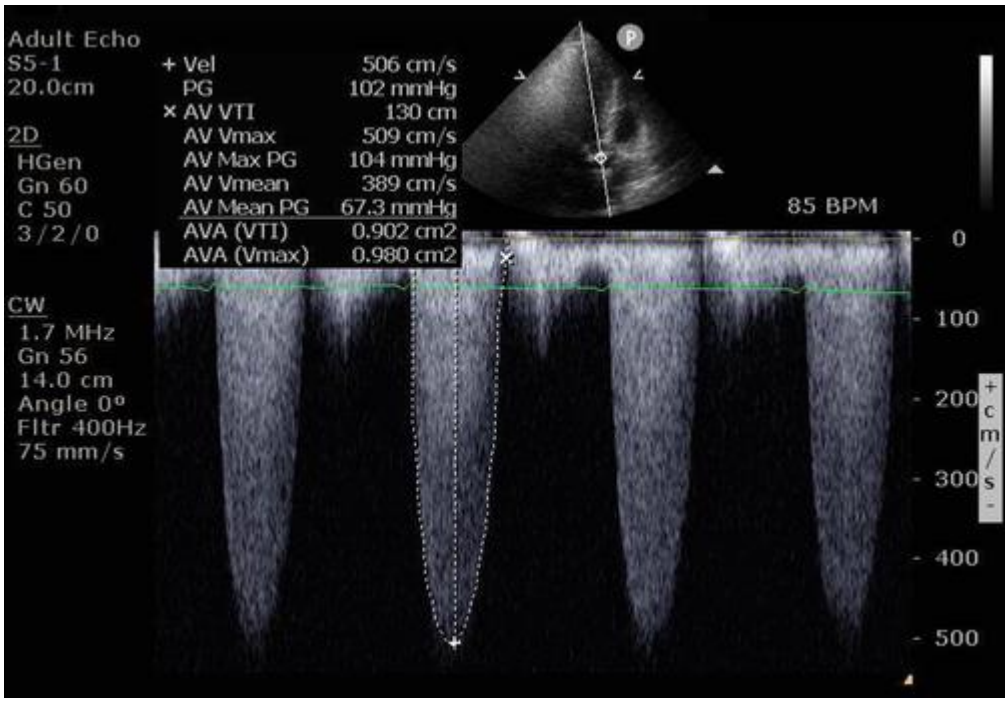


Figure 4

Spectral Doppler Bioprosthetic AV Replacement Aortic Stenosis, Late Second Trimester

Pressure half time was 148 ms, mean AV replacement gradient was 67 mm Hg, and there was severe stenosis and regurgitation. Vel = velocity; other abbreviations as in **Figures 1** and **2**.

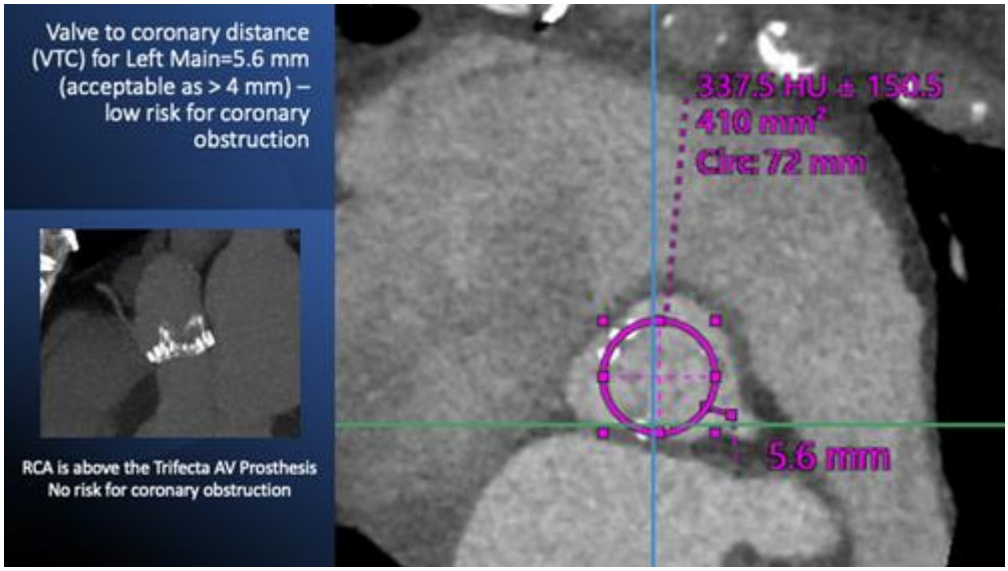


Figure 5

Dose Reduced TAVR CT to Evaluate Size and Coronary Height for Valve in Valve TAVR

Dose-reduced computed tomography transcatheter aortic valve replacement for valve size and coronary distance for valve-in-valve planning within degenerated bioprosthetic aortic valve replacement. Coronary height was acceptable with no risk for coronary obstruction, valve circumference of 72 mm acceptable for a 26 mm Medtronic CoreValve Evolut. RCA = right coronary artery.

At 30 weeks' gestation, she was admitted for worsening heart failure and shortness of breath, with BNP >1000 pg/mL. She was diuresed with intravenous furosemide but had worsening symptoms. From a fetal standpoint, there was appropriate fetal growth in the 56th percentile for gestational age and normal amniotic fluid volume. She had continued worsening heart failure not responding to intravenous furosemide. She was reclassified as mWHO IV and considered high maternal risk. Due to severe clinical decompensation, she underwent urgent valve-in-valve TAVR for severe bioprosthetic AVR regurgitation.

Both the cardio-obstetrics program team and the valve team managed the patient in preparation for TAVR at 30 weeks and 4 days' gestation. The patient

was intubated intraoperatively for transesophageal echocardiography (TEE) guidance. A perinatologist was present during her procedure in case urgent delivery was indicated for fetal distress. She had prophylactic emergency vascular access placed prior to anesthesia induction in case she decompensated. Invasive hemodynamics initially were left ventricular systolic pressure 220 mm Hg, end-diastolic pressure 58 mm Hg, and aortic pressure 148/90 mm Hg. After deployment of a 26-mm Medtronic CoreValve Evolut bioprosthesis TAVR, hemodynamics showed left ventricular systolic pressure 100 mm Hg, end-diastolic pressure 20 mm Hg, aortic pressure 90/60 mm Hg, and mean gradient across the aortic valve 8 mm Hg (**Videos 5 to 10**). No complications occurred. She was extubated same day, further diuresed, and discharged home after 9 days. She was seen back in the cardio-obstetrics program clinic and closely followed post valve-in-valve TAVR. Her mWHO score dropped at time of delivery to II or III. She underwent a term induction of labor at 37 weeks and 4 days' gestation and had a successful vaginal delivery of a healthy female infant. Her postpartum course was uncomplicated.

Question 1: Describe a multidisciplinary cardio-obstetrics program?

A cardio-obstetrics program involves multidisciplinary management of pregnant patients. Patients are evaluated in the preconception period to assess risk for pregnancy, decrease cardiometabolic risk factors, as well as evaluating and substituting teratogenic medications. Patients are then managed through pregnancy with follow-up based on cardiac risk scoring schema. Cardio-obstetrics program meetings are held with the multidisciplinary team in order to develop delivery plans prior to 28 weeks' gestation. The team is made up of cardiologists with expertise in cardio-obstetrics, perinatologists, electrophysiologists, obstetrician-gynecologists, pharmacists, social workers, obstetric anesthesiologists, cardiac anesthesiologists, cardiothoracic surgeons, neonatologists, hospitalists, and nurse coordinators. Team-based management of pregnant patients is critical to prevent maternal morbidity and mortality.[1,2] cardio-obstetrics program

clinics are associated with decreased adverse cardiac complications in pregnancy.[1]

Question 2: How does mWHO risk stratification help manage patients in cardio-obstetrics program?

Several risk stratification models exist, including the CARPREG II (Canadian Cardiac Disease in Pregnancy) expanded risk score and the mWHO classification. Data demonstrate that risk stratification can predict not only pregnancy-associated adverse outcomes, but also long-term cardiac outcomes in the highest risk categories. The risk stratification schema also predicts fetal outcomes. Utilizing mWHO criteria predicts which patients can be managed and delivered at local hospitals vs those who require close monitoring and intervention during pregnancy at expert centers. For pregnant patients at the highest risk, cardio-obstetrics program will monitor serially, recommend changes to delivery location and mode of delivery, and provide other considerations for the delivering obstetric team.[3-5]

Question 3: How does valvular heart disease impact risk during pregnancy?

Valvular heart disease in pregnancy is linked to adverse outcomes. In pregnant patients with both mechanical heart valves and bioprosthetic heart valves, there is an increase in major adverse cardiac events, hypertensive disorders of pregnancy, and ante/postpartum hemorrhage, as well as an increase in duration of hospitalization and cost. Fetal outcomes, including stillbirth, are also increased. There is no significant difference in maternal outcomes between mechanical and bioprosthetic heart valves.[6] Invasive interventions may be needed in severe hemodynamic deterioration of valvular disease. Catheter-based interventions are an alternative to surgery during pregnancy. Patients who need catheter-based intervention should be evaluated and managed in a multidisciplinary fashion. Procedures should be carried out at experienced centers. To date, valve-in-valve TAVR for bioprosthetic degeneration in pregnancy has been completed in a few cases

and limited outcome information is available, but there appears to be short-term safety and efficacy of this intervention.[7]

Question 4: Does BNP aid in the management of pregnant patients?

Hemodynamic changes in pregnancy may lead to maladaptation in pregnant patients with cardiac disease or with an underlying susceptibility to cardiac decompensation. N-terminal pro–B-type natriuretic peptide (NT-proBNP) and BNP are released in cardiomyocyte stretch, myocardial dysfunction, and increased circulating volume. NT-proBNP and BNP are the gold standard in biomarker evaluation for heart failure. In healthy pregnancy with no cardiac dysfunction, NT-proBNP and BNP are stable through all trimesters and postpartum. Both retain their negative predictive value to exclude heart failure in pregnancy. NT-proBNP and BNP can be followed through pregnancy in patients with cardiac lesions at increased risk for heart failure, pre-existing cardiomyopathy, and maternal congenital heart disease. As they should remain stable through trimesters, a significant increase may signal worsening heart failure.

NT-proBNP and BNP increase in patients with preeclampsia. Higher concentrations are seen in early onset and severe preeclampsia. In evaluation of peripartum cardiomyopathy, NT-proBNP and BNP help with diagnosis, and higher levels are associated with worse prognosis. During pregnancy, measurements of NT-proBNP and BNP with signs and symptoms of heart failure may help guide management.[8]

Question 5: What are factors to consider when imaging the pregnant patient?

TTE is the mainstay for evaluating cardiac conditions in the pregnant patient. The American College of Obstetrics and Gynecology recommends that TTE be performed in all pregnant women with any cardiac diagnosis. Serial evaluation is recommended for valvular and congenital disorders. TTE is considered safe for both the pregnant patient and fetus. TEE in the pregnant patient may have increased risk of emesis and aspiration due to decreased gastric motility,

increased relaxation of the lower esophageal sphincter, and increased intra-abdominal pressure. After 18 weeks, pregnant patients are considered “full stomach.” Risk and benefits of a TEE must be weighed. Endotracheal intubation is often recommended for TEE after 18 weeks due to the increased risk for aspiration. Fetal considerations for the administration of anesthesia for TEE include fetal hypoxia, possible fetal sedation or distress, and miscarriage/preterm birth; however, routine anesthetics are not teratogenic. Anesthesia/TEE should be pursued if the study alters outcome. Maternal and fetal monitoring should be considered in all procedures after fetal viability or gestational age >22 to 24 weeks, with plans in place for delivery if fetal distress is encountered. CT scanning leads to fetal exposure of ionizing radiation. Doses typically used in clinical practice are well below the threshold for fetal anomalies, intellectual disability, or childhood leukemia.[9] Fetal exposure to radiation should be minimized and appropriate shielding should be used. Shared decision for both CT scanning and TEE should be undertaken. In the setting of management of valve in valve, there is limited utility for 2-dimensional/3-dimensional TEE for valve sizing compared with CT. Undersizing TAVR in pregnancy may lead to worse outcomes; thus, CT scanning may be needed.[10,11]

4. Clinical Outcomes by Sex After Pulsed Field Ablation of Atrial Fibrillation

IMPORTANCE

Previous studies evaluating the association of patient sex with clinical outcomes using conventional thermal ablative modalities for atrial fibrillation (AF) such as radiofrequency or cryoablation are controversial due to mixed results. Pulsed field ablation (PFA) is a novel AF ablation energy modality that has demonstrated preferential myocardial tissue ablation with a unique safety profile.

OBJECTIVE

To compare sex differences in patients undergoing PFA for AF in the Multinational Survey on the Methods, Efficacy, and Safety on the Postapproval Clinical Use of Pulsed Field Ablation (MANIFEST-PF) registry.

DESIGN, SETTING, AND PARTICIPANTS

This was a retrospective cohort study of MANIFEST-PF registry data, which included consecutive patients undergoing postregulatory approval treatment with PFA to treat AF between March 2021 and May 2022 with a median follow-up of 1 year. MANIFEST-PF is a multinational, retrospectively analyzed, prospectively enrolled patient-level registry including 24 European centers. The study included all consecutive registry patients (age ≥18 years) who underwent first-ever PFA for paroxysmal or persistent AF.

EXPOSURE

PFA was performed on patients with AF. All patients underwent pulmonary vein isolation and additional ablation, which was performed at the discretion of the operator.

MAIN OUTCOMES AND MEASURES

The primary effectiveness outcome was freedom from clinically documented atrial arrhythmia for 30 seconds or longer after a 3-month blanking period. The primary safety outcome was the composite of acute (<7 days postprocedure) and chronic (>7 days) major adverse events (MAEs).

RESULTS

Of 1568 patients (mean [SD] age, 64.5 [11.5] years; 1015 male [64.7%]) with AF who underwent PFA, female patients, as compared with male patients, were older (mean [SD] age, 68 [10] years vs 62 [12] years; P < .001), had more paroxysmal AF (70.2% [388 of 553] vs 62.4% [633 of 1015]; P = .002) but had fewer comorbidities such as coronary disease (9% [38 of 553] vs 15.9% [129 of 1015]; P < .001), heart failure (10.5% [58 of 553] vs 16.6% [168 of 1015]; P = .001), and sleep apnea (4.7% [18 of 553] vs 11.7% [84 of 1015]; P < .001). Pulmonary vein isolation was performed in 99.8% of female (552 of 553) and 98.9% of male (1004 of 1015; P = .90) patients. Additional ablation was

performed in 22.4% of female (124 of 553) and 23.1% of male (235 of 1015; P = .79) patients. The 1-year Kaplan-Meier estimate for freedom from atrial arrhythmia was similar in male and female patients (79.0%; 95% CI, 76.3%-81.5% vs 76.3%; 95% CI, 72.5%-79.8%; P = .28). There was also no significant difference in acute major AEs between groups (male, 1.5% [16 of 1015] vs female, 2.5% [14 of 553]; P = .19).

CONCLUSION AND RELEVANCE

Results of this cohort study suggest that after PFA for AF, there were no significant sex differences in clinical effectiveness or safety events.

5. Outcomes of Abbreviated vs Standard DAPT by Sex in Patients at High Bleeding Risk

IMPORTANCE

Abbreviated dual antiplatelet therapy (DAPT) reduces bleeding with no increase in ischemic events in patients at high bleeding risk (HBR) undergoing percutaneous coronary intervention (PCI).

OBJECTIVES

To evaluate the association of sex with the comparative effectiveness of abbreviated vs standard DAPT in patients with HBR.

DESIGN, SETTING, AND PATIENTS

This prespecified subgroup comparative effectiveness analysis followed the Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated vs Standard DAPT Regimen (MASTER DAPT) trial, a multicenter, randomized, open-label clinical trial conducted at 140 sites in 30 countries and performed from February 28, 2017, to December 5, 2019. A total of 4579 patients with HBR were randomized at 1 month after PCI to abbreviated or standard DAPT. Data were analyzed from July 1 to October 31, 2022.

INTERVENTIONS

Abbreviated (immediate DAPT discontinuation, followed by single APT for ≥6 months) or standard (DAPT for ≥2 additional months, followed by single APT for 11 months) treatment groups.

MAIN OUTCOMES AND MEASURES

One-year net adverse clinical events (NACEs) (a composite of death due to any cause, myocardial infarction, stroke, or major bleeding), major adverse cardiac or cerebral events (MACCEs) (a composite of death due to any cause, myocardial infarction, or stroke), and major or clinically relevant nonmajor bleeding (MCB).

RESULTS

Of the 4579 patients included in the analysis, 1408 (30.7%) were women and 3171 (69.3%) were men (mean [SD] age, 76.0 [8.7] years). Ischemic and bleeding events were similar between sexes. Abbreviated DAPT was associated with comparable NACE rates in men (hazard ratio [HR], 0.97 [95% CI, 0.75-1.24]) and women (HR, 0.87 [95% CI, 0.60-1.26]; P = .65 for interaction). There was evidence of heterogeneity of treatment effect by sex for MACCEs, with a trend toward benefit in women (HR, 0.68 [95% CI, 0.44-1.05]) but not in men (HR, 1.17 [95% CI, 0.88-1.55]; P = .04 for interaction). There was no significant interaction for MCB across sex, although the benefit with abbreviated DAPT was relatively greater in men (HR, 0.65 [95% CI, 0.50-0.84]) than in women (HR, 0.77 [95% CI, 0.53-1.12]; P = .46 for interaction). Results remained consistent in patients with acute coronary syndrome and/or complex PCI.

CONCLUSIONS AND RELEVANCE

These findings suggest that women with HBR did not experience higher rates of ischemic or bleeding events compared with men and may derive particular benefit from abbreviated compared with standard DAPT owing to these numerically lower rates of events.

6. CT Surgery Needs Universal Policies for Pregnancy and Family Leave, Survey Shows

Female cardiothoracic surgeons have fewer children and are more likely to face infertility when compared with their male counterparts, according to new survey data. Additionally, when female surgeons are pregnant, they experience a higher than typical rate of pregnancy complications.

Family planning and medical training are established mutual obstacles because they typically occur at the same time in a trainee's life. Achieving balance often comes at an understood cost, especially for women, but at the 2024 Society of Thoracic Surgeons (STS) meeting, leaders in the field argued that systemic changes need to be made to attract the best future surgeons.

"The proportion of women is increasing [in cardiothoracic surgery], but I think an inclusive environment that allows surgeons of both genders to have the work and family life that they want is important for recruitment, retention, [and] overall wellbeing of the workforce," Anna Olds, MD (University of Southern California, Los Angeles), who shared the data in two presentations at STS 2024, told TCTMD. "And we want surgeons to be happy—we want people to be happy and come to work because we're helping other people."

STS President Jennifer Romano, MD (University of Michigan Congenital Heart Center, Ann Arbor), who co-chaired the session, highlighted the importance of bringing greater awareness to these issues.

"So many of us went into this specialty without necessarily even thinking about the fact that it could potentially impact our ability to have a family," she told TCTMD. "I've learned that if you ask, if you speak up, quite often it's not a matter of 'people don't want [to help],' it's that they don't know [how]. So the more that we inform people and educate those around us, really can impart change. It's pretty simple."

Survey Results

For the first survey, Olds and colleagues polled STS and Women in Thoracic Surgery trainee and surgeon members between January and June 2023, with males instructed to answer pregnancy questions regarding their nonsurgeon childbearing partners. In all, 378 people sent in complete responses, of whom 45.8% were female, 75.1% were academic/academic-affiliated, and 20.1% were trainees.

Compared with men, more female cardiothoracic surgeons were single or never married (19.1% vs 5.9%) and fewer had spouses who did not work outside the home (9.6% vs 21.8%). Additionally, women were less likely to have children (56.7% vs 85.4%) and to have fewer children on average than male surgeons (1.9 vs 2.5; $P < 0.001$ for all).

Fewer female surgeons said they had the number of children they wanted naturally without assisted reproductive technologies, fertility, and surrogacy (37.8% vs 63.4%; $P = 0.001$). About one-third of women reported using infertility testing or assisted reproductive technologies, with fewer than one in five men saying they'd turned to these tools.

Strikingly, 41.6% of female respondents said their desire to have children deterred them from pursuing cardiothoracic surgery, compared with only 22.9% of males ($P = 0.004$).

Pregnancy loss was reported by 42% of all female respondents, which is substantially higher than the estimated rate of 20-25% in the general population, Olds stated. Notably, 70.5% of these women took no time off after their miscarriage. "It is unclear if this is due to fear of judgement and stigma from colleagues, or part of the traditional surgical culture where personal needs often come second to patient care," she said. "These challenges with starting a family may limit recruitment of talented female candidates into the field of cardiothoracic surgery."

These challenges with starting a family may limit recruitment of talented female candidates into the field of cardiothoracic surgery. Anna Olds

In her second presentation, Olds showed more data from 255 respondents (63% male) who had had at least one live birth. Female cardiothoracic surgeons were on average 3 years older than female nonsurgeons at first live birth (34.5 vs 31.5 years; $P < 0.001$). Additionally, more surgeons used assisted reproductive technologies than nonsurgeons (31.2% vs 15.4%; $P = 0.003$) and they were also more likely to work more than 60 hours per week during pregnancy (70.3% vs 14.1%; $P < 0.001$).

Almost half of all female surgeons (45.2%) reported a major pregnancy complication compared to only 27.2% of nonsurgeons (27.2%; $P = 0.003$), including higher rates of preeclampsia and preterm labor or preterm premature rupture of membranes.

Among the 93 female surgeons surveyed, only 18.3% said they had a reduced work schedule during pregnancy. Slightly more than half (51.3%) of those who chose a regular workload said they would have liked to cut back their hours but didn't because of a fear of stigma or judgement of weakness (52.7%), concern about burdening colleagues (44.6%), or employer disapproval (31.1%). Additionally, 78.5% worked more than four overnight call shifts per month and 72.0% worked at least 12 hours in the operating room per week during their last trimester.

Among all respondents, being age 35 years or older and being a female surgeon were associated with major pregnancy complications in a multivariate analysis. When the model was limited to female surgeons alone, working at least 12 hours per week in the OR during the last trimester was an additional risk factor.

"This study highlighted a need to develop formal policies to protect the maternal-fetal health of female cardiothoracic surgeons, protect autonomy in family planning timeline decisions for surgeons and trainees, and provide education about pregnancy in surgeons," Olds said. "This is particularly applicable to women surgeons as older age is a risk factor for worse pregnancy outcomes."

Need for a National Policy

Until recently, parental leave policies in cardiothoracic surgery training—and most other fields of medical education—had been largely institution-based. In 2020, the American Board of Thoracic Surgery instituted a specialty-wide policy that guarantees one 6-week leave for all trainees (two for those in an integrated program). However, many feel that this still is not enough.

Leading the charge at her institution, Romano created the "most lenient" policy for pregnant and lactating trainees in the field, she said during the discussion. "It allows for 12 weeks regardless of gender for any type of parental leave or major medical illness, and it does not extend your duration of training," Romano explained. "It was amazing, when I presented it . . . unanimously everybody applauded. All the directors were like 'We should have thought of this years ago.'" The fact that this idea had not occurred to administrators is why the policy was needed, she added.

"My dream would be that one day this is an ACGME policy for everybody, for all female residents, and in other specialties too," Olds said. "Having that level of support and having written policies—formal written policies—is crucial because then everyone knows what to expect."

Commenting during the session, Douglas Wood, MD (University of Washington, Seattle), a former STS president, agreed that having a "gender neutral" formalized policy will reduce stigma and benefit all. "If you're in a power situation in this room, go home and develop a policy," he urged. "If you're . . . a trainee, go home and get an ally and ask: 'Can you develop policies and can I help with them?' If it's written down and makes clear the expectations and what the rules are, it makes it easier for everyone to understand and [is] much more equitable."

Romano's advice for anyone looking to follow in her footsteps would be to bring in a visiting professor like herself to help educate both trainees and higher-level executives at an institution.

“Everywhere I go and give this talk, it gets that message out there,” she said. “It somewhat drives my husband crazy because I share a lot of information. I went through 12 cycles of IVF and had my children at 42 and 44 and feel so very blessed to have them, but it was not an easy journey, and I did it when it wasn't okay to talk about it.”

Working to enact national level policies regarding pregnancy and parental leave is a priority for the STS, Romano said. “It's not fair that trainees and junior faculty members need to be fighting this over and over again at an institutional or a state level,” she said. “There are a lot of other things that also impact our female trainees as well as faculty, but the more that we can help them take this battle to the right place, the better.”

7. Assisted Reproductive Technology Linked to Higher Stroke Risk

Women who have used assisted reproductive technology (ART) appear to be at higher risk for stroke when it comes time to deliver a baby, according to a large observational study.

After accounting for stroke risk factors, those who had an ART code in their record at the time of the delivery hospitalization had significantly higher rates of any stroke, acute ischemic stroke, subarachnoid hemorrhage, and intracerebral hemorrhage compared with those without prior use of ART, Alis Dicpinigaitis, MD (NewYork-Presbyterian/Weill Cornell Medical Center, New York, NY), reported here at the International Stroke Conference.

And among patients who had a stroke during the delivery hospitalization, those with a history of ART were more likely to die and had longer hospital stays, results that hint at increased stroke severity, Dicpinigaitis said.

He put the findings, which were published simultaneously online in Stroke, into the context of the beneficial impact of ART for women seeking to have children.

“It’s important to stipulate that we don’t think that ART is an overwhelmingly dangerous therapy, nor do we want to dissuade people interested in pursuing ART to not pursue it,” Dicpinigaitis said. “Instead, we advocate for counseling older patients who are planning to receive it and for those who have risk factors for stroke to initiate appropriate treatments and, additionally, to adequately control known stroke triggers during hospitalization like psychological distress as well as the development of infection.”

Potential Risks With ART

Dicpinigaitis said ART, which encompasses intrauterine insemination and various methods of in vitro fertilization, is generally considered safe, although there are potential risks and complications. Those include vascular adverse events like hypertensive disorders of pregnancy and venous thromboembolism. The possible mechanism underlying these events is the estrogen surge that occurs during ART, resulting in persistent hormonal imbalances that produce changes in coagulation, hemodynamics, and hemostasis, he suggested.

Because the handful of studies that have examined links between ART and cerebrovascular disease have provided mixed results, he and his colleagues decided to explore the issue further using data from the National Inpatient Sample, which gathers information on hospitalizations in the United States.

The analysis included more than 19.1 million delivery hospitalizations for women ages 15 to 55 that occurred between 2015 and 2020. Overall, 1.1% included a code for ART. Patients with a history of ART versus those without tended to be older and were more likely to be white, to have private insurance, and to have higher income. They also had higher rates of CV comorbidities and stroke risk factors.

Before adjustment, ART was associated with higher rates (per 100,000 person-years) of the following events:

- Any stroke (27.1 vs 9.1)

- Acute ischemic stroke (9.9 vs 3.3)
- Subarachnoid hemorrhage (7.4 vs 1.6)
- Intracerebral hemorrhage (7.4 vs 2.2)
- Cerebral venous thrombosis (7.5 vs 2.7)

The investigators used inverse probability weighting to adjust for potential confounders, and found that the likelihood of all of those events—except for cerebral venous thrombosis—remained higher in the ART group:

- Any stroke (adjusted OR 2.14; 95% CI 2.02-2.26)
- Acute ischemic stroke (adjusted OR 2.75; 95% CI 2.51-3.02)
- Subarachnoid hemorrhage (adjusted OR 3.83; 95% CI 3.38-4.33)
- Intracerebral hemorrhage (adjusted OR 5.37; 95% CI 4.82-5.98)
- Cerebral venous thrombosis (adjusted OR 0.82; 95% CI 0.72-0.93)

A subgroup analysis by age demonstrated that stroke was significantly more common in women with a history of ART irrespective of whether they were older or younger than 35, confirming the findings of the main analysis, Dicpinigaitis said.

ART Is Safe Overall

Eliza Miller, MD (NewYork-Presbyterian/Columbia University Irving Medical Center, New York, NY), who was not involved in the study, underscored that "ART is a safe treatment that helps a lot of people," adding that "the last thing I would want people to do is not go through that when they want to have a child because of the fear that they'll have a stroke."

She told TCTMD that it's difficult to draw too many conclusions from a study like this because it relies on administrative data. In this case, for instance, it's unclear how well coding captures the number of people who have used ART, complicating interpretation.

The last thing I would want people to do is not go through [ART] when they want to have a child because of the fear that they'll have a stroke. Eliza Miller

"I think that it deserves more investigation, but I think that it's quite possible that this may be overestimating the effects a little bit because of the potential that those who experience a complication are more likely to have that code recorded in the billing data," Miller said, noting that some patients who use ART but don't have a complication during the delivery may not have that history of ART recorded.

She pointed out, too, that this study cannot establish a causal relationship between ART and stroke. "It may be that the same factors that led the patients to need ART in the first place also put them at risk for stroke," she cautioned.

Stroke, which very rarely occurs during a delivery hospitalization, is one of many complications for which women who use ART will be at increased risk, Miller said. "It's just another reason to make sure that you're getting really excellent care from a high-risk maternal-fetal medicine specialist during your pregnancy and watching for warning signs that could indicate risk of stroke—for example, higher blood pressure—toward the end of pregnancy."

8. Sex Disparities in Longitudinal Use and Intensification of GDMTs Among Patients With Newly Diagnosed HFrEF

BACKGROUND

Guideline-directed medical therapies (GDMTs) are the mainstay of treatment for heart failure with reduced ejection fraction (HFrEF), but they are underused. Whether sex differences exist in the initiation and intensification of GDMT for newly diagnosed HFrEF is not well established.

METHODS

Patients with incident HFrEF were identified from the 2016 to 2020 Optum deidentified Clinformatics Data Mart Database, which is derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans. The primary outcome was the use of optimal GDMT within 12 months of HFrEF diagnosis. Consistent with the guideline recommendations during the time period of the study, optimal GDMT was defined as ≥50% of the target dose of evidence-based beta-blocker plus ≥50% of the target dose of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, or any dose of angiotensin receptor neprilysin inhibitor plus any dose of mineralocorticoid receptor antagonist. The probability of achieving optimal GDMT on follow-up and predictors of optimal GDMT were evaluated with time-to-event analysis with adjusted Cox proportional hazard models.

RESULTS

The study cohort included 63 759 patients (mean age, 71.3 years; 15.2% non-Hispanic Black race; 56.6% male). Optimal GDMT use was achieved by 6.2% of patients at 12 months after diagnosis. Female (compared with male) patients with HFrEF had lower use across every GDMT class and lower use of optimal GDMT at each time point at follow-up. In an adjusted Cox model, female sex was associated with a 23% lower probability of achieving optimal GDMT after diagnosis (hazard ratio [HR], 0.77 [95% CI, 0.71-0.83]; P<0.001). The sex disparities in GDMT use after HFrEF diagnosis were most pronounced among patients with commercial insurance (females compared with males; HR, 0.66 [95% CI, 0.58-0.76]) compared with Medicare (HR, 0.85 [95% CI, 0.77-0.92]); $P_{interaction}$ sex×insurance status=0.005) and for younger patients (age <65 years: HR, 0.65 [95% CI, 0.58-0.74]) compared with older patients (age ≥65 years: HR, 87 [95% CI, 80-96]) $P_{interaction}$ sex×age=0.009).

CONCLUSIONS

Overall use of optimal GDMT after HFrEF diagnosis was low, with significantly lower use among female (compared with male) patients. These findings

highlight the need for implementation efforts directed at improving GDMT initiation and titration.

9. Complex Congenital Heart Disease and Congenital Uterine Anomalies Impacting Pregnancy Outcomes

Introduction

Congenital uterine anomalies (CUAs), also known as müllerian anomalies, are a known risk factor for obstetrical complications such as premature delivery and miscarriage.[1] Complex congenital heart disease (CCHD), such as heterotaxy and single-ventricle disease, is often accompanied by extracardiac manifestations; however, the exact correlation and significance of genitourinary involvement remain unclear. We present a case series of 3 patients with palliated CCHD who had pregnancies complicated by premature delivery and were subsequently found to have CUAs that may have contributed to their obstetrical complications.

Learning Objectives

- To understand the association of extracardiac anatomical malformations, such as CUAs, in CCHD.
- To appreciate how CUAs may augment obstetrical risk in patients with CCHD.
- To consider screening patients with CCHD who are undergoing prepregnancy counseling for CUAs with pelvic MRI.

Case 1

A 32-year-old G1P0000 woman with a history of congenitally corrected transposition of the great arteries with a restrictive ventricular septal defect and pulmonary valve stenosis status post hemi-Mustard baffle, a Rastelli-type left ventricle-to- aorta tunnel, a bidirectional Glenn procedure, and a right ventricle-to-pulmonary artery 28-mm conduit homograft, type 1 diabetes

managed with an insulin pump, and atrial fibrillation status post ablation presented at 35 weeks' gestation with preterm premature rupture of the membranes and preeclampsia with severe features, and ultimately failed induction necessitating emergency cesarean delivery. At the time of delivery, she was found to have a bicornuate uterus. She had an unremarkable postpartum course. She later had 2 further pregnancies; both deliveries were premature but were otherwise uncomplicated.

Case 2

A 27-year-old G2P0010 woman with a history of tricuspid atresia status post lateral tunnel Fontan procedure at age 2 years, coarctation of the aorta status post- stent placement at age 17 years, atrial septal defect, fenestration closure at age 21 years after a thrombotic stroke, and Fontan-associated liver disease with high-grade fibrosis (F3) presented at 32 weeks' gestation with loss of fetal movement and was found to have nonreassuring fetal heart tones necessitating emergency cesarean delivery. At the time of delivery, she was found to have a bicornuate uterus. The hysterotomy incision inadvertently involved a portion of her abnormal septum and complicated her initial postpartum course with postpartum hemorrhage; however, she ultimately returned to her cardiac baseline.

Case 3

A 24-year-old G3P0020 woman with a history of heterotaxy with asplenia and right atrial appendage isomerism, hypoplastic left heart syndrome, double-outlet right ventricle, and interrupted inferior vena cava status post Kawashima-type Fontan procedure, Fontan-associated liver disease with high-grade fibrosis (F3), and 2 previous miscarriages, presented at 23 weeks' gestation with concern for shortened cervical length and uterine didelphys. She was initially managed expectantly until she went into preterm labor at 28 weeks with concern for footling breech presentation, necessitating emergency cesarean delivery. At the time of delivery, she was found actually to have

bicornuate uterus. Her postpartum course was notable for postpartum depression but was otherwise uncomplicated.

Discussion

As has been increasingly recognized, patients with CCHD phenotypes that were previously not survivable into adulthood are now able to undergo a variety of complex palliative surgical procedures that have dramatically improved their survival. With this improvement has come an increasing number of patients with CCHD who desire pregnancy and a search to characterize their risk and likelihood of success so we may best counsel them. Although guidelines are robust with regard to their recommendations for cardiac work-up and treatment, there is little about extracardiac manifestations that are common with these patients and may affect their ability to both achieve pregnancy and carry it to term.[2,3]

CUAs, also known as müllerian duct anomalies, are a wide spectrum of anatomical malformations of the uterus. The underlying pathophysiology involves disruption of the normal embryologic development of the uterus somewhere in the process of differentiation, migration, unification, and canalization of the müllerian duct system. Although there is no universally accepted classification system for CUAs, the 2021 American Society for Reproductive Medicine classification system is the accepted standard in the United States and divides these anomalies on this embryologic basis while accounting for the wide variety of manifestations (**Figure 1**).[4,5] Each subtype carries different obstetrical considerations (**Table 1**).[1] CUAs are best evaluated by magnetic resonance imaging (MRI) because it can define both external and internal contours of the uterus; however, CUAs are often first suspected on the basis of pelvic ultrasound or, as in 2 of our cases, found at the time of delivery.[6] Furthermore, CUAs may complicate cesarean delivery, thus adding further risk to already complicated deliveries and even damage to an already anatomically malformed uterus, as seen in case 2.

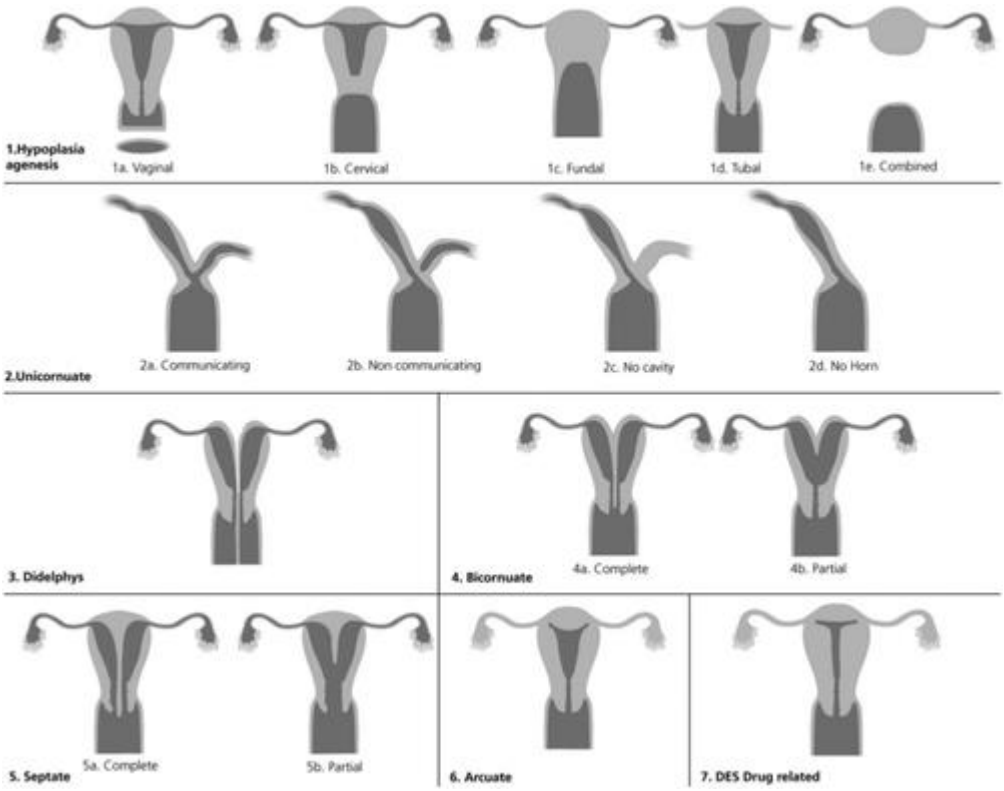


Figure 1

Spectrum of Congenital Uterine Anomalies

Congenital uterine anomalies (CUAs) can be categorized into the following broad categories on the basis of the timing of disruption of normal embryologic development of the Müllerian ducts. This figure actually simplifies many of the anomalies, which were further delineated in the 2021 American Society for Reproductive Medicine guidelines, as referenced in the text. Reprinted with permission from Behr et al[5]. DES = diethylstilbestrol.

Table 1Obstetrical Complications of Congenital Uterine Anomalies

Area of Embryologic Disruption	Congenital Uterine Anomaly	Obstetrical Complications
Hypoplasia/agenesis	—	Infertility

Table 1 Obstetrical Complications of Congenital Uterine Anomalies

Area of Embryologic Disruption	Congenital Uterine Anomaly	Obstetrical Complications
Unification	Unicornuate	Miscarriage, prematurity, fetal malpresentation, ectopic pregnancy
	Bicornuate	Miscarriage, prematurity, and fetal malpresentation
	Didelphys	Prematurity
Canalization	Septate	Miscarriage, prematurity, and fetal malpresentation
	Arcuate	Second trimester pregnancy loss, fetal malpresentation

The most common association of CUAs is with renal malformations, most commonly unilateral renal agenesis or multicystic dysplastic kidney.[6] Only 1 recent case series has looked specifically at the association between CUAs and CCHD, by presenting 8 patients with a majority single ventricle or transposition patients with unification defects.[7] No larger studies exist that describe the prevalence of CUAs in persons with congenital heart disease, nor are there any studies looking at the compounded obstetrical risk that having both may conditions carry. Although one may hypothesize an association between genetic syndromes and the concomitant presence of CUA and CCHD, none of our 3 patients had an identified genetic syndrome. It may be reasonable to offer genetic counseling and consider genetic testing for these patients, as noted in the 2018 American Heart Association and American College of Cardiology guideline for management of adults with congenital heart disease, because this may be missed in patients with CCHD where it is not phenotypically apparent.[8]

In the most recent systemic review on pregnancy outcomes in patients with a Fontan circulation, Garcia Ropero et al[9] showed that there was a high incidence of miscarriages, prematurity, and intrauterine growth restriction. These investigators wrote that this is "driven by a combination of factors, including placental insufficiency, intrinsic morphological uterine abnormalities, and adverse hemodynamics related to the Fontan circulation"[9]; however no dedicated studies have looked at the prevalence of CUAs in these patients. Other subtypes of CCHD such as heterotaxy do not have as robust studies on obstetrical outcomes, although similar complications can be expected for similar reasons. In our cases, determining which factors affected their premature deliveries to what extent is difficult given the known association of premature delivery with their forms of CCHD. In all 3 cases, limitations in cardiac output augmentation were compounded by placental abnormalities that have been shown to be associated with CCHD.[10] Furthermore, although CUAs are known risk factors for prematurity and miscarriage, there may also be a yet undefined disruption in postnatal uterine development in patients with prolonged or profound cyanosis that may affect the ability of the uterus to carry pregnancy, as well as increase the risk of complications such as postpartum hemorrhage.

Overall, these cases are hypothesis generating for an underappreciated association between CCHD and CUAs. It may be reasonable to consider uterine imaging for CUAs, ideally with MRI, as part of prepregnancy planning and risk stratification in patients with CCHD who desire pregnancy, especially if there is a history of spontaneous abortions, as was the case with 2 of our patients. Further research is needed to better describe the prevalence of CUAs with CCHD and identify more specific associations that may allow for better pregnancy counseling as more patients from this group continue to age and become of child-bearing potential.

10. Preeclampsia-Associated Cardiovascular Risk Factors at 6 and 24 Months After Pregnancy

BACKGROUND

Increased cardiovascular risk following preeclampsia is well established and there are signs of early cardiovascular aging 6 months postpartum. This study assessed whether blood pressure (BP) and other cardiovascular measures are abnormal 2 years postpartum in the same cohort to determine ongoing risk markers.

METHODS

Six months and 2 years postpartum, BP was measured using sphygmomanometry, 24-hour ambulatory BP monitoring, and noninvasive central BP. Anthropometric measures, blood, and urine biochemistry were performed. Cross-sectional comparisons between preeclampsia and normotensive pregnancy (NP) groups and longitudinal comparisons within each group were made at 6 months and 2 years.

RESULTS

Two years postpartum, 129 NP, and 52 preeclampsia women were studied who also had 6 months measures. At both time points, preeclampsia group had significantly higher BP (office BP 2 years, 112±12/72±8 versus 104±9/67±7 mm Hg NP; [P<0.001]; mean ambulatory BP monitoring 116±9/73±8 versus 106±8/67±6 mm Hg NP; [P<0.001]). No significant BP changes noted 6 months to 2 years within either group. Office BP thresholds of 140 mm Hg systolic and 90 mm Hg diastolic classified 2% preeclampsia and 0% NP at 2 years. American Heart Association 2017 criteria (above normal, >120/80 mm Hg) classified 25% versus 8% (P<0.002), as did our reference range threshold of 122/79 mm Hg. American Heart Association criteria classified 60% post-preeclampsia versus 16% after NP with above-normal ambulatory BP monitoring (P<0.001). Other cardiovascular risk markers more common 2 years post-preeclampsia included higher body mass index (median 26.6 versus 23.1, P=0.003) and insulin resistance.

CONCLUSIONS

After preeclampsia, women have significantly higher BP 6 months and 2 years postpartum, and have higher body mass index and insulin-resistance scores, increasing their future cardiovascular risk. Regular cardiovascular risk screening should be implemented for all who have experienced preeclampsia.

11. **Effect of Insomnia and Short Sleep Duration on Incident CVD Events Among Women**

Women traversing midlife are highly vulnerable to sleep disturbances, with nearly one in two women experiencing sleep apnea, insomnia, and/or short sleep durations. Because poor sleep is now recognized as an important independent determinant of cardiovascular disease (CVD), the sleep deterioration manifested by midlife women may be implicated in their increased risk of CVD emerging in those years. Yet, there is a paucity of evidence on this subject.

To address this gap, Thurston and colleagues investigated the association between trajectories of poor sleep and incident CVD in women in midlife from the Study of Women's Health Across the Nation. The study involved a large diverse sample of pre- and peri-menopausal women who were 42 to 52 years of age and free of CVD at baseline (N = 2964). Data from up to 16 visits over more than two decades of follow-up were available, including repeated assessment of self-reported sleep duration, symptoms of insomnia, and new CV events (including myocardial infarction, heart failure, revascularization procedures, cerebrovascular accidents, or CV death). By tracking changes in sleep patterns over time, the authors could derive longitudinal sleep trajectories, which yielded a unique value to the predictive modeling. The results of multivariable analysis accounting for demographics and atherosclerotic CVD risk score showed that women who reported persistently high insomnia symptoms had a 1.71-fold (95% CI, 1.19–2.46) greater risk of future CVD than those with persistently low insomnia symptoms. This association withstood adjustments for multiple covariates, including snoring,

depression, and vasomotor symptoms. Conversely, trajectories of changing insomnia symptoms through the 22-year follow-up period, irrespective of the direction of change, were not predictive of incident CVD. The hazard ratios for new-onset CVD in those with persistently short sleep durations were also significantly greater than the hazard ratios in those with persistently moderate sleep duration; however, further correction for the atherosclerotic CVD risk score attenuated the strength of the relationship (HR, 1.51; 95% CI, 0.98–2.33). It is noteworthy that women who reported both persistently high insomnia symptoms and short sleep durations exhibited the highest risk of developing CVD (HR, 1.75; 95% CI, 1.03–2.98). This is consistent with a growing body of literature indicating that insomnia with short sleep duration is the most detrimental insomnia phenotype.

To summarize, this study shows that chronic exposure to insomnia and, to a lesser degree, to short sleep durations, is associated with a heightened vulnerability to CVD in women in midlife. An important next step would be to identify the mechanisms underlying these relationships. As midlife includes the menopause transition, the role of fluctuations in the hormonal milieu warrants investigation. This study also sets the ground for targeted interventions to test whether improving sleep among women in midlife improves their CV prognosis.

12. Sex Differences in Association of Physical Activity With All-Cause and Cardiovascular Mortality

Introduction

Although greater amounts of physical activity (PA) are associated with well-known reductions in cardiovascular and all-cause mortality, fewer than one-quarter of all Americans meet the minimum guidelines for PA[1] as recommended by the Centers for Disease Control and Prevention (CDC),[2] and the American Heart Association/American College of Cardiology.[3] Both sets of guidelines recommend a minimum 150 min/wk of moderate PA or 75 min/wk

of vigorous PA, in addition to at least 2 days of muscle strengthening activities per week. While these recommendations are the same for male and female individuals,[2] it has been long known that female individuals persistently lag behind male individuals in PA engagement—manifesting a "gender gap" that begins early in life and continues throughout adulthood.[4,5] The extent to which this gap in levels of PA engagement may translate into differences in outcomes has been unclear. There are long-established and well-recognized sex differences in the physiologic response to PA, in thresholds of exercise tolerance, and in overall exercise capacity.[6,7] Thus, it is possible that the degree of health benefit derived from PA could differ between sexes based on frequency, duration, intensity, and type of exercise. Understanding any such differences could inform efforts to close the "gender gap" and optimize PA-related outcomes for all.

Methods

All data and materials are publicly available from the CDC National Center for Health Statistics and are accessible online.[8] The National Center for Health Statistics Disclosure Review Board approved the National Health Interview Survey (NHIS) study.[9] Data analyses for this study were additionally approved by the Cedars-Sinai Medical Center institutional review board.

Study sample

The CDC and the National Center for Health Statistics have conducted the NHIS with data collected from all 50 states and the District of Columbia (**Supplemental Methods**).[10,11] We pooled data from a total of 646,279 adult participants of the NHIS from years 1997 to 2017 and linked their records to National Death Index records through December 31, 2019. We excluded participants with preexisting diagnoses of coronary heart disease, myocardial infarction, stroke, emphysema, chronic bronchitis, or cancer (n = 120,200), limitations in activities of daily living (n = 6,332), missing data on PA (n = 23,975), or missing data on follow-up status or key covariates (n = 63,651). We further excluded individuals with outcomes occurring within the first 2

years of follow-up (n = 19,708) to minimize the potential of reverse causation bias. The remaining 412,413 participants comprised our study sample.

PA, clinical, and outcomes data

At each survey, a consistent set of standardized questions was used to ascertain frequency, duration, and type of regular PA engagement (**Supplemental Methods**).[12,13] The frequency of the activity (times/wk) was multiplied by duration of the activity to provide the minutes per week of aerobic PA. To account for intensity, total weighted moderate-to-vigorous intensity aerobic physical activity (MVPA) was obtained by summing the duration of moderate intensity plus vigorous intensity multiplied by 2.[14,15] Data were also collected on sociodemographic characteristics, medical comorbidities, and self-rated health status (**Supplemental Methods**). All participants were under surveillance for all-cause and cardiovascular death.[16]

Statistical analyses

For the primary outcomes analyses, we examined the association of PA measures with mortality using Cox proportional hazard regression models that accounted for the complex multistage sampling design of the survey (ie, using weight, primary sampling units, and strata)[17] and adjusted for covariates including age, race/ethnicity, body mass index, smoking status, hypertension, diabetes mellitus, alcohol consumption, education, income-to-poverty ratio, marriage status, access to medical care, self-reported health status, and chronic disease conditions. Before entering the model, unweighted PA measures were expanded using restricted cubic spline given potential nonlinear relationships. Sex differences in the associations between PA measures and mortality were assessed using likelihood ratio tests between models with and without parameters representing the interaction between sex and the cubic spline variables representing PA. The level of PA measure at which the maximal benefit was achieved for men was considered as the comparator referent. We secondarily assessed level of aerobic PA engagement based on frequency, duration per session, and intensity, where intensity was

calculated as the proportion of vigorous PA out of total MVPA. Specifically, participants were categorized as physically inactive (<150 min/wk of MVPA) or physically active (≥150 min/wk of MVPA), per the 2018 PA guideline.[2] Physically active participants were then categorized by frequency, duration per session, and intensity of aerobic PA, and inactive participants were considered the referent for all analyses. Similarly, participants were also categorized by muscle strengthening activity as physically inactive (<2 sessions/wk) or physically active (≥2 sessions/wk). We then repeated multivariable-adjusted Cox models, as described previously, to examine sex-specific associations for these categorized PA measures. We used the adjusted Wald test to evaluate the sex interaction by including the multiplicative terms of PA and sex.

In secondary analyses, we repeated analyses for women and men stratified by age grouped by decade or 2 decades. To account for the previously reported tendency of women to underreport PA duration compared with men,[18] we conducted secondary analyses that incorporated sex-specific PA duration weights applied to both women (ie, multiplied by 1.2) and men (ie, multiplied by 0.8) (**Supplemental Methods**). We also repeated analyses assessing for any sex differences in outcomes associated with aerobic and muscle strengthening activity combined. To contextualize observed PA associations with mortality, we examined associations of PA with prevalent major risk factors (ie, hypertension, diabetes) and measures of self-reported health (**Supplemental Methods**). In exploratory analyses, to assess whether sex-specific associations may have changed over time, we also repeated the primary analyses while considering PA data collected during 2007 (instead of 1997) as the "baseline" assessment in relation to outcomes surveillance data collected through 2017. All analyses were performed using R v4.2.1 and STATA v16. A 2-tailed P value <0.05 was considered significant.

Results

Of the 412,413 participants in our study, 54.7% were women, 14.4% identified as Black, and 18.4% identified as Hispanic. The mean age was 43.9 ± 16.6

years and other baseline characteristics are shown in **Table 1**. Frequency and distribution of characteristics by sex were similar for participants included in our analyses when compared with those who were excluded (**Supplemental Table 1**). Over a total 4,911,178 person-years of follow-up, there occurred 39,935 all-cause deaths (8.1 per 1,000 person-years) including 11,670 cardiovascular deaths (2.4 per 1,000 person-years).

Table 1Characteristics of the Study Participants

	Frequency and Proportion[a]		**P Value**
	Women (n = 225,689)	**Men (n = 186,724)**	
Age, y			<0.001
18-44	122,559 (56.1)	106,129 (59.0)	
45-64	67,989 (31.2)	60,290 (32.2)	
65-85	35,141 (12.5)	20,305 (8.6)	
Race and ethnicity			<0.001
Hispanic	41,974 (13.7)	34,099 (14.8)	
Non-Hispanic Black	35,806 (12.6)	23,725 (11.0)	
Non-Hispanic White	135,435 (67.9)	117,985 (68.6)	
Other[b]	12,474 (5.6)	10,915 (5.4)	
Education level			0.089

Table 1Characteristics of the Study Participants

	Frequency and Proportion[a]		P Value
	Women (n = 225,689)	**Men (n = 186,724)**	
<High school degree	39,731 (14.9)	32,710 (16.1)	
High school degree	53,978 (24.3)	44,833 (24.6)	
>High school degree	131,221 (60.4)	108,470 (58.8)	
Body mass index, kg/m^2			<0.001
<25	106,095 (48.7)	60,120 (32.0)	
25-29	66,069 (28.5)	83,499 (44.2)	
≥30	53,525 (22.7)	43,105 (23.7)	
Hypertension	51,741 (20.9)	40,741 (20.8)	<0.001
Diabetes	12,545 (4.9)	10,365 (5.1)	0.92
Smoking status			<0.001
Never	148,904 (66.1)	100,307 (55.1)	

Table 1Characteristics of the Study Participants

	Frequency and Proportion[a]		P Value
	Women (n = 225,689)	**Men (n = 186,724)**	
Former	37,290 (16.6)	42,121 (21.9)	
Current	39,326 (17.1)	44,130 (22.8)	
Alcohol use, d/wk			<0.001
0	169,389 (74.0)	102,651 (55.7)	
1	25,796 (11.8)	32,075 (17.0)	
≥2	30,504 (14.1)	51,998 (27.1)	
Chronic conditions, n			<0.001
0	151,369 (68.7)	129,007 (69.7)	
1	59,425 (25.3)	46,717 (24.7)	
≥2	14,895 (5.9)	11,000 (5.4)	
Self-rated health			<0.001
Excellent	70,560 (33.2)	64,287 (36.1)	

Table 1Characteristics of the Study Participants

	Frequency and Proportion[a]		P Value
	Women (n = 225,689)	**Men (n = 186,724)**	
Very good	77,895 (34.8)	65,037 (34.8)	
Good	58,034 (24.5)	44,102 (22.8)	
Fair/Poor	16,395 (6.3)	11,361 (5.3)	
Access to medical care[c]	198,110 (88.3)	143,277 (78.0)	<0.001
Marriage status			<0.001
Never married	49,859 (20.1)	50,983 (25.0)	
Married/living with partner	115,146 (61.8)	104,940 (64.7)	
Widowed/divorced/separated	60,237 (17.8)	30,485 (10.1)	
Unknown	447 (0.1)	316 (0.1)	
Income-to-poverty ratio[d]			<0.001
<1	33,977 (11.1)	20,311 (8.7)	
1-1.99	39,120 (15.1)	28,061 (13.6)	

Table 1Characteristics of the Study Participants

	Frequency and Proportion[a]		P Value
	Women (n = 225,689)	**Men (n = 186,724)**	
≥2	122,754 (60.7)	116,877 (66.0)	
Other[e]	29,838 (12.9)	21,475 (11.6)	

Values are n (%).

BMI = body mass index; DM = diabetes mellitus.

a Analyses of percent values were conducted using the adjustment of weights, primary sampling units, and strata. Variable categories may not sum to 100% because of truncation and unspecified category (ie, refused, not ascertained, or don't know).

b This category included American Indian or Alaska Native; Native Hawaiian or other Pacific Islander; Asian; Hispanic or Latino; mixed races; refused to respond; or race unknown.

c Place of usual source of medical care included clinic or health center, doctor's office, hospital emergency room, hospital outpatient department, and some other places.

d Income-to-poverty ratio was calculated by dividing top-coded total combined imputed family income by the U.S. Census Bureau's poverty thresholds.

e This category included unknown and undefinable conditions.

Sex differences in aerobic PA associations with all-cause mortality

The baseline characteristics of physically active participants are shown in **Supplemental Table 2**. Overall, 32.5% of women and 43.1% of men regularly engaged in aerobic PA, and all major measures of PA were significantly more frequent in men (**Table 2**) (P for all <0.001). In particular, regular engagement for women and men was 10.3% and 15.2% for MPA (≥150 min/wk) and was 28.3% and 38.9% for VPA (≥75 min/wk), respectively. For women, regular PA compared with inactivity was associated with a 24% lower risk of all-cause mortality (HR: 0.76; 95% CI: 0.73- 0.80). For men, regular PA compared with inactivity was associated with a reduction in all-cause mortality by 15% (HR: 0.85; 95% CI: 0.82-0.89), and this magnitude of benefit was significantly less than that seen for women (**Table 3**) (Wald test, F = 12.0, P < 0.001 for interaction).

Table 2PA Type and Duration in NHIS Participants

	Female	**Male**
MVPA, min/wk		
Mean value	206	353
<150	155,978 (67.3)	107,065 (56.4)
150-299	20,423 (9.6)	18,731 (10.3)
≥300	49,288 (22.9)	60,928 (33.1)
MPA, min/wk		
Mean value	53	84
<150	203,584 (89.6)	158,610 (84.7)
150-299	12,785 (6.0)	14,115 (7.6)
≥300	9,320 (4.3)	13,999 (7.5)
VPA, min/wk		

Table 2PA Type and Duration in NHIS Participants

	Female	Male
Mean value	76	135
<75	164,914 (71.5)	115,272 (60.9)
75-149	23,305 (10.9)	21,944 (12.1)
≥150	37,470 (17.4)	49,508 (26.8)
Intensity (VPA/MVPA), %[b]		
Mean value	29.3	38.7
<25	644 (0.3)	974 (0.5)
25-49	3,356 (1.5)	3,900 (2.1)
50-74	27,296 (12.9)	28,031 (15.3)
75-100	38,415 (17.8)	46,754 (25.5)
Muscle strengthening PA, sessions/wk		
Mean value	0.85	1.25
0	182,984 (79.9)	135,443 (72.0)
2-3	26,574 (12.5)	27,932 (15.3)
4-5	7,982 (3.8)	12,075 (6.5)
≥6	8,149 (3.6)	11,274 (6.0)

Values are n (%) or mean.

MPA = moderate intensity physical activity; MVPA = moderate-to-vigorous intensity physical activity; NHIS = National Health Interview Survey; PA = physical activity; VPA = vigorous intensity physical activity.

a Analyses of percent values and mean values account for the complex multistage sample design of the survey using weights, primary sampling units, and strata. Variable categories may not sum to 100% because of truncation.

b Only physically active participants (ie, MVPA>0 min/wk) were shown.

Table 3Association of PA With All-Cause Mortality by Sex

	Female		**Male**		**P for Interaction**
	HR (95% CI)	**P Value**	**HR (95% CI)**	**P Value**	
Aerobic PA					
Inactive	Referent	—	Referent	—	
Active[a]	0.76 (0.73-0.80)	<0.001	0.85 (0.82-0.89)	<0.001	<0.001
Frequency, sessions/wk					
Inactive	Referent	—	Referent	—	
1-5	0.71 (0.65-0.76)	<0.001	0.84 (0.78-0.89)	<0.001	<0.001
6-9	0.74 (0.70-0.79)	<0.001	0.83 (0.78-0.88)	<0.001	
≥10	0.80 (0.76-0.85)	<0.001	0.85 (0.80-0.90)	<0.001	
Duration of session, min					

Table 3Association of PA With All-Cause Mortality by Sex

	Female		Male		P for Interaction
	HR (95% CI)	P Value	HR (95% CI)	P Value	
Inactive	Referent	—	Referent	—	
<15	0.80 (0.75-0.86)	<0.001	0.84 (0.79-0.89)	<0.001	0.063
15-29	0.84 (0.77-0.91)	<0.001	0.91 (0.84-0.98)	0.025	
30-59	0.73 (0.69-0.78)	<0.001	0.78 (0.74-0.83)	<0.001	
≥60	0.78 (0.73-0.83)	<0.001	0.79 (0.74-0.85)	<0.001	
Intensity (VPA/MVPA), %					
Inactive	Referent	—	Referent	—	
<25	0.65 (0.51-0.81)	<0.001	0.78 (0.64-0.96)	0.020	0.007
25-49	0.70 (0.62-0.79)	<0.001	0.81 (0.73-0.90)	<0.001	
50-74	0.75 (0.71-0.80)	<0.001	0.83 (0.78-0.88)	<0.001	
75-100	0.78 (0.75-0.82)	<0.001	0.82 (0.78-0.86)	<0.001	
Muscle strengthening activity					

Table 3Association of PA With All-Cause Mortality by Sex

	Female		Male		P for Interaction
	HR (95% CI)	P Value	HR (95% CI)	P Value	
Inactive	Referent	—	Referent	—	
Active[a]	0.81 (0.76-0.85)	<0.001	0.89 (0.85-0.94)	<0.001	0.005
Frequency, sessions/wk					
Inactive	Referent	—	Referent	—	
2-3	0.74 (0.69-0.80)	<0.001	0.86 (0.81-0.92)	<0.001	<0.001
4-5	0.80 (0.73-0.88)	<0.001	0.89 (0.81-0.97)	0.014	
≥6	0.91 (0.85-0.98)	0.008	0.96 (0.90-1.03)	0.27	

All models accounted for the multistaged survey sample design and were adjusted for total MVPA, muscle strengthening PA (ie, frequency), and covariates that included age, race/ethnicity, body mass index, smoking status, hypertension, diabetes mellitus, alcohol consumption, education, income-to-poverty ratio, marriage status, access to medical care, self-rated health, and chronic disease conditions.

Abbreviations as in **Table 2**.

a Physically active adults were then stratified by frequency, duration, and intensity of PA.

In dose-dependent analyses for the entire cohort, the benefit of PA on all-cause mortality peaked at ~300 min/wk of MVPA and then plateaued

(**Supplemental Figure 1**). The greatest mortality benefit in men was achieved at 300 min/wk of MVPA with an 18% lower hazard in all-cause mortality. Women derived a similar magnitude of benefit at 140 min/wk of MVPA, and continued to benefit with increasing min/wk of MVPA until the greatest benefit of 24% lower hazard (HR: 0.76; 95% CI: 0.72-0.80) was achieved at ~300 min/wk (**Figure 1**). When examining the relationship specifically for VPA and all-cause mortality, the sex difference was also significant: the greatest benefit was seen in men who engaged in 110 min/wk of VPA, with a 19% lower hazard in all-cause mortality (HR: 0.81; 95% CI: 0.77-0.85); by comparison, women derived the same benefit from only 57 min/wk of VPA (likelihood ratio test, chi-square = 12.8, P = 0.004). Although the benefit of VPA reached a plateau beyond 110 min/wk in men, further benefit was derived from more min/wk of VPA in women (**Supplemental Figure 2**). For women, the 110 min/wk of VPA was associated with 24% lower hazard for all-cause mortality (HR: 0.76; 95% CI: 0.72-0.80) and although the absolute maximum benefit for women was reached at 120 min/wk, the corresponding risk reduction was similar at 24% lower hazard (HR: 0.76; 95% CI: 0.72-0.79). Similarly, for MPA, women appeared to derive a greater mortality benefit per unit time spent engaging in this level of PA: for men the maximal benefit was seen at 90 min/wk of MPA with a 20% reduction in all-cause mortality (HR: 0.80; 95% CI: 0.75-0.84), and for women the same magnitude of benefit was seen at 50 min/wk of MPA (HR: 0.79; 95% CI: 0.75-0.84) (**Supplemental Figure 2**) although the interaction term for this sex difference did not reach statistical significance (likelihood ratio test, chi-square = 3.85, P = 0.27). For women, 90 min/wk of MPA was associated with 24% lower hazard for all-cause mortality (HR: 0.76; 95% CI: 0.71-0.80) and although the maximum benefit for women was reached at 97 min/wk of MPA, the corresponding risk reduction was similar at 24% lower hazard (HR: 0.76; 95% CI: 0.71-0.80).

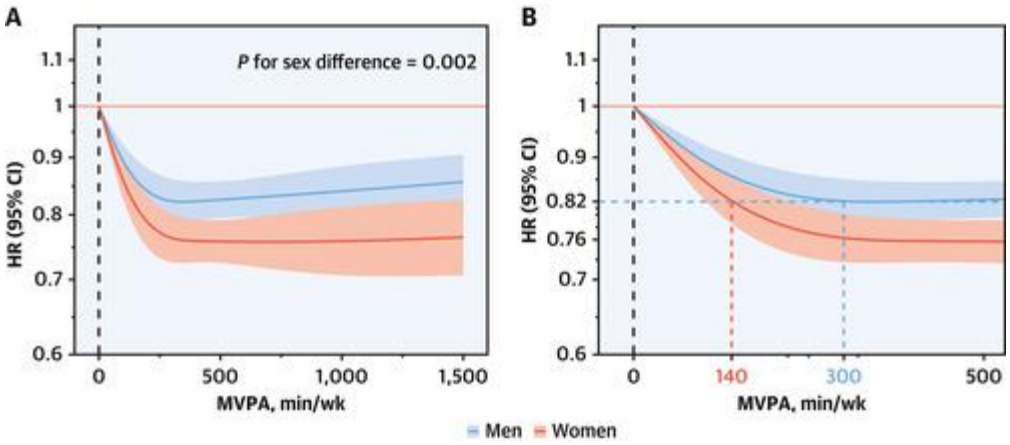


Figure 1

Sex-Specific Association of MVPA With All-Cause Mortality

The multivariable-adjusted association of moderate-to-vigorous intensity aerobic physical activity (MVPA) duration with all-cause mortality is shown by sex overall (A) and with focused comparison on the maximal survival benefit achieved for female compared with male individuals (B).

Sex differences in muscle strengthening activity associations with all-cause mortality

Men compared with women were more likely to engage in muscle strengthening PA and with greater frequency (**Table 2**). Overall, 19.9 % of women and 27.8 % of men reported engaging in any regular muscle strengthening PA, with fewer sessions for women (average 0.85 sessions/wk) than men (average 1.25 sessions/wk). For men who performed regular muscle strengthening PA compared with inactivity, mortality risk was reduced by 11% (HR: 0.89; 95% CI: 0.85-0.94); for women, the mortality risk reduction was 19% (HR: 0.81; 95% CI: 0.76-0.85) and this sex difference was significant (**Table 3**) (Wald test, F = 7.9, P = 0.005 for interaction). In dose-dependent analyses, men derived the greatest mortality benefit from engaging in 3 sessions/wk of muscle strengthening PA with a 14% lower hazard in all-cause mortality; women derived equivalent or greater benefit by engaging in only a single muscle strengthening PA per week (**Figure 2**). For women compared

with men engaging in 3 sessions/wk of muscle strengthening PA, there was ~2-fold greater relative reduction in all-cause mortality.

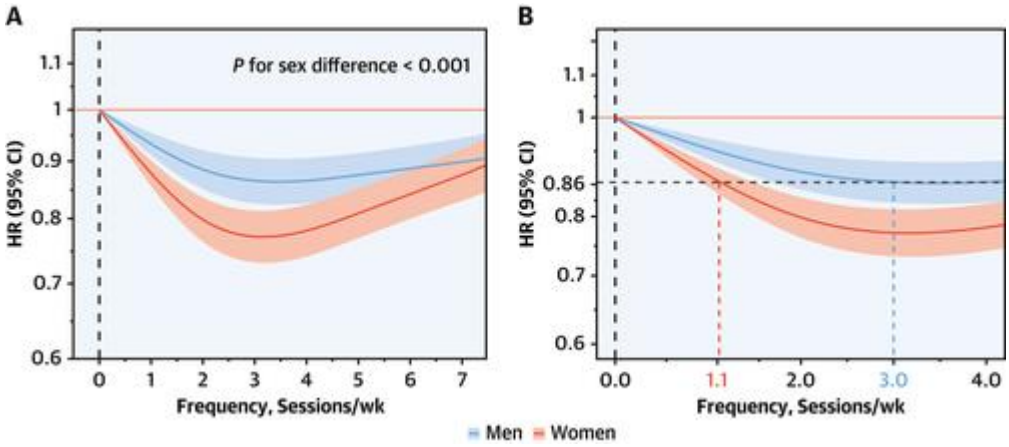


Figure 2

Sex-Specific Association of Muscle Strengthening Physical Activity With All-Cause Mortality

The multivariable-adjusted association of muscle strengthening frequency with all-cause mortality is shown by sex overall (A) and with focused comparison on the maximal survival benefit achieved for female compared with male individuals (B).

Sex differences in PA associations with cardiovascular mortality

For cardiovascular mortality, engaging in regular aerobic PA compared with inactivity was associated with a risk reduction of 14% (HR: 0.86; 95% CI: 0.80-0.93) for men and 36% (HR: 0.64; 95% CI: 0.58-0.71) for women; this sex difference was significant (Wald test, F = 18.8, P < 0.001 for interaction) (**Supplemental Table 3**). Similarly, engaging in regular muscle strengthening activities compared with inactivity was associated with a cardiovascular risk reduction of 11% (HR: 0.89; 95% CI: 0.80-0.98) in men and 30% (HR: 0.70; 95% CI: 0.62-0.78) in women, and this 3-fold relative sex difference was also significant (Wald test, F = 9.9, P = 0.001 for interaction) (**Supplemental Table 3**).

Secondary analyses

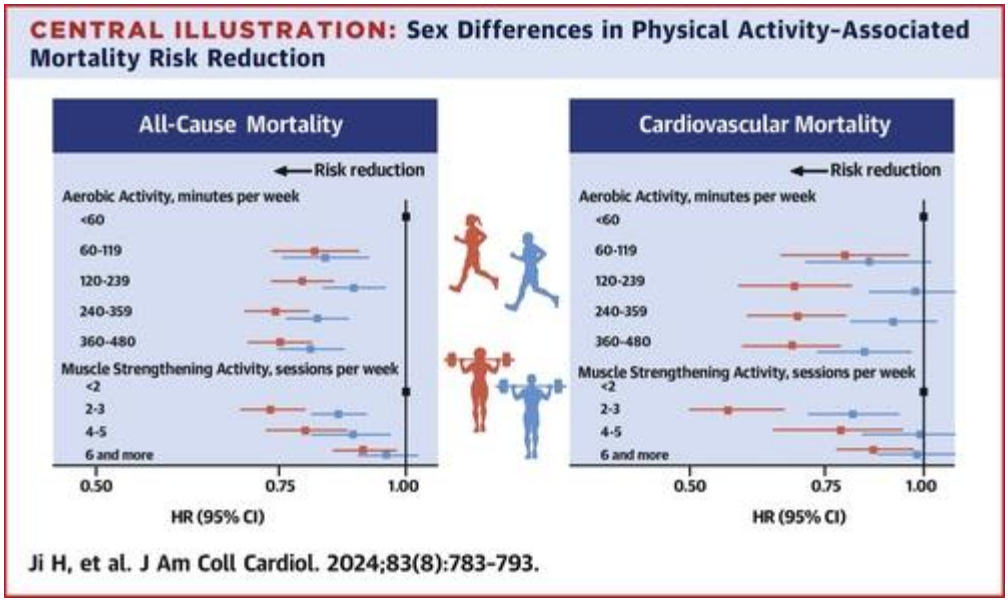
Across measures of aerobic PA frequency, duration per session, and intensity, the relative magnitude of survival benefit was consistently higher in women than in men for all-cause and cardiovascular mortality (**Table 3**, **Supplemental Table 3**). Because of slight variations in the questions related to PA in the NHIS 1997 survey, compared with the surveys from subsequent years, we conducted sensitivity analyses excluding participant data from 1997 and findings remained consistent (**Supplemental Table 4**). In analyses that age-stratified results by decade and then by 2 decades (**Supplemental Tables 5** and **6**), the magnitude of PA-related mortality risk reduction was consistently greater in women than men particularly for middle-aged individuals (ie, age 40-59 years, $P < 0.05$ for interaction); within the age <40 or ≥60-year strata, the magnitude of sex difference was attenuated ($P > 0.05$ for interaction) (**Supplemental Tables 5** and **6**). In secondary analyses accounting for potential underreporting of PA in women compared with men, results were consistent with those of primary analyses (**Supplemental Table 7**, **Supplemental Figure 3**). When considering regular engagement in both aerobic PA and muscle strengthening activity combined, in an additive manner, we observed slightly greater risk reduction in women (HR: 0.72; 95% CI: 0.67-0.87) and men (HR: 0.76; 95% CI: 0.71-0.87) for all-cause mortality although this difference was not statistically significant (**Supplemental Table 8**). In analyses of PA and self-reported health status, we found that both aerobic PA and muscle strengthening PA were associated with lower odds of self-rated poorer health, indicating a positive relationship with perceived quality of life; these associations also did not significantly differ by sex (**Supplemental Table 9**). In cross-sectional analyses of PA and risk factors, we found that PA engagement was associated with lower odds of prevalent diabetes in both sexes, to varying degrees (**Supplemental Table 10**). Interestingly, PA engagement was associated with lower odds of prevalent hypertension in women but higher odds in men; notwithstanding the limitations of cross-sectional analyses, this finding may represent reverse causality (ie, men with a diagnosis of hypertension may be more motivated to exercise).

Exploratory analyses

To examine the extent to which sex-specific associations may have changed over time, we repeated analyses of PA measures and all-cause mortality while considering 2007 as the "baseline" year of PA data collection (instead of year 1997) with ~10 years of outcomes surveillance through 2017 (instead of ~20 years' surveillance). Results of these analyses were similar in directionality of sex difference to those of the primary analyses for both overall aerobic PA and muscle strengthening activity measures, although the magnitude of differences was attenuated in the setting of fewer events accrued per category over the shorter follow-up period (**Supplemental Table 11**).

Discussion

In a population-scale nationally representative cohort of U.S. adults, we observed evidence of substantial sex differences in the relations of self-reported leisure-time PA with survival benefit. Although both sexes achieved a peak survival benefit at 300 minutes of weekly aerobic MVPA, women derived a 24% mortality reduction that was substantially greater than for men who derived an 18% mortality reduction from the same degree of regular exercise; similarly, for any given dose of PA leading up to 300 min/wk, women derived proportionately greater benefits than men. These findings were evident for both all-cause and cardiovascular-specific mortality. Importantly, the greater magnitude of PA-related survival benefit in women than men was consistently found across varied measures and types of PA including frequency, duration per session, and intensity of aerobic PA, as well as frequency of muscle strengthening activities. Our results from this large representative population study not only highlight a sex differential response in health benefits from PA but suggest that women stand to especially gain in reduction of cardiovascular and all-cause mortality risk (**Central Illustration**). Such findings could be used to further motivate engagement in PA among currently less engaged segments of the female population and particularly those individuals for whom time represents a barrier to exercise.



Central Illustration

Sex Differences in Physical Activity–Associated Mortality Risk Reduction

We studied 412,413 U.S. adults and found that women compared with men derived greater gains in all-cause and cardiovascular mortality risk reduction from equivalent doses of leisure-time physical activity.

Prior data on sex differences in PA-associated outcomes are limited. In a Taiwanese cohort study of 199,265 male and 216,910 female individuals, designed to identify the minimum amount of exercise needed to reduce all-cause mortality, both sexes derived a similar 14% risk reduction in association with as little as 15 minutes of moderate intensity activity per day or 90 min/wk.[19] Consistent with these findings, our results also showed that all-cause mortality benefit was comparable between sexes at similarly lower doses of exercise. Extending from these findings, we further found that sex differences emerged at higher doses of exercise. With respect to cardiovascular outcomes, a meta-analysis of 33 studies showed that relative risk for coronary heart disease was 2-fold lower for female individuals compared with male individuals at similar levels of PA, with a significant sex interaction.[20] Our study adds to these findings by demonstrating similar sex differences in PA-associated risk for not only incident disease but also cardiovascular mortality.

There are several potential explanations for our findings. It has long been known that male individuals have measurably greater exercise capacity than female individuals across all ages.[6,7,21] This may be in part due to attributes including on average proportionately larger hearts, wider lung airways, greater lung diffusion capacity, and larger muscle fibers in male compared with female individuals.[22-24] In particular, men have ~38% more lean body mass compared with women,[23] and so a relatively lower absolute limit to exercise-induced vasodilatory capacity imposed by substantially lower lean mass and muscle mass in women may be proportionately more efficiently improved by strengthened muscle from PA and especially from muscle strengthening PA of the same dose.[25] Indeed, this phenomenon could underlie the marked sex differences in mortality risk reduction seen from equivalent frequencies of muscle strengthening activity. In fact, physiology studies have demonstrated that female individuals exhibit greater vascular conductance and blood flow during exercise, with female individuals having a higher density of capillaries per unit of skeletal muscle when compared with male individuals.[26] Accordingly, although female individuals have generally lower muscle strength at baseline, when both male and female individuals undergo strength training, female individuals experience greater relative improvements in strength, which is a stronger predictor of mortality than muscle mass.[27,28] Furthermore, sexual dimorphism at the level of muscle fiber type and muscle fiber metabolic, contractile, and dynamic function may also contribute to sex differential responses to the same dose of PA.[29] For example, male individuals have a greater proportion of type II glycolytic muscle fibers, whereas female individuals have a greater proportion of type I oxidative fibers.[30,31] These differences could contribute to not only the known greater female sensitivity to disuse atrophy[32] but also, conversely, the greater female sensitivity to PA observed in our study. We did note an age-interaction such that the female benefit appeared to be attenuated in older compared with younger age; further research may discern whether this finding is related to the menopausal transition with or without hormone replacement therapy taken by some women. Notably, in age-stratified analyses, sex differences were most pronounced for middle-aged adults (ie, ages 40 to 59 years) and this

finding aligns with the wealth of prior evidence indicating that relative differences in cardiovascular risk factor burden in middle age are highly impactful on not just later but overall life-long risks for adverse outcomes.[33]

Notwithstanding the need to validate our results in separate studies and using complementary measures of PA exposure and response, our findings have several implications. The longstanding conventional assumption has been that male and female individuals across all age groups should engage in the same amount of regular PA to gain the same benefit.[5] This assumption has motivated public health attention on the frequently observed "PA gap" between female and male individuals,[5] wherein female individuals are from childhood onward consistently found to be approximately 6% to 10% less physically active than their male counterparts.[34,35] Our findings suggest that attention to the "PA gap" may benefit from a greater emphasis on equalizing levels of engagement rather than equalizing specific dose exposures. Large studies of European children have shown that male individuals consistently perform better on tests of muscular strength, power, and endurance, as well as speed-agility and exercise capacity, whereas female individuals perform better on flexibility measures.[36] In adults, at least one study has shown that the predicted exercise capacity assessed from a Bruce protocol treadmill stress test should be adjusted lower for women than for men, in relation to all-cause as well as cardiovascular death.[7] In the context of prior studies, our findings indicate that female individuals stand to gain proportionately more than male individuals in reduction of cardiovascular and all-cause mortality risk for a given dose of regular exercise. Although existing PA guidelines currently offer sex-agnostic recommendations,[2,3] sex-specific considerations could enhance individual risk assessments and tailored exercise prescriptions in the effort to increase engagement in PA especially for female individuals.

Study limitations

Several limitations of our study merit consideration. First, all PA data collected were self-reported, albeit using a standardized questionnaire that remained stable over time.[12,13] Numerous PA studies have examined the validity of

similarly standardized questionnaire data and found generally acceptable reliability and moderate validity.[37] Objective measures of PA, using devices such as accelerometers or wearables, are increasingly feasible but still incur substantial costs and so the availability of such data linked to outcomes across diverse populations remain limited.[38] Fortunately, a degree of external validity for the PA data collected in the current analysis is also provided by separate studies that used accelerometry and observed the magnitude and significance of mortality associations to be consistent with our results.[39] Although our analyses considered the potential effects of sex differences in self-reported PA level, additional studies are needed to further investigate how variable recall bias may influence the extent to which benefits from PA can differ by sex. Although the primary focus of this analysis was on leisure-time PA, unmeasured variation in household or other activities that can vary by sex could yet have contributed to outcome differences. When estimating muscle strengthening activities, the only information collected was the frequency and not the duration of such activity; nonetheless, this type of reporting is consistent with the 2018 U.S. guidelines on PA that simply recommend performing muscle strengthening activities at least twice weekly without mention of duration.[2] In addition, the NHIS collects aerobic PA data based on exercise occurring for at least 10 minutes and benefits can be derived from periods of PA shorter than 10 minutes. Similarly, the NHIS data on muscle strengthening activities were limited to questions on lifting weights or doing calisthenics. Given the observational design of the study, causal relationships cannot be presumed and results should be interpreted with caution. To mitigate the effects of potential confounding, we excluded participants who were censored within the first 2 years of follow-up for initial analysis. However, unmeasured confounders could yet have influenced results including differential reporting by male and female individuals, unassessed health status factors, and variations in PA engagement over time. Although our sampling methods aimed to reduce the likelihood of reverse causation, we cannot entirely rule out its possible influence in the analyses. Although our exploratory analyses suggest that sex-specific outcomes likely persisted throughout the 2 decades of outcomes surveillance studied, trends

in PA engagement continue to evolve and will warrant future additional studies.[12]

Conclusions

We found evidence of significant sex differences in association of self-reported leisure-time PA with all-cause and cardiovascular death in a large nationally representative cohort of U.S. adults followed for >4 million person-years. Overall, women compared with men derived greater gains in all-cause and cardiovascular mortality risk reduction from equivalent doses of leisure-time PA. These findings could motivate efforts to close the "gender gap" by encouraging especially women to engage in any regular leisure-time PA. Our findings extend from a continually growing body of concordant evidence from physiology and clinical studies on sexual dimorphism in exercise capacity and associated outcomes. Taken together, the results from the current study combined with those of prior investigations suggest that PA-related risk assessments and recommendations could benefit from sex-specific considerations; in turn, sex-specific guidance could serve to motivate increased PA engagement particularly among women who stand to gain substantial health benefits. Recognizing the limitations of a one-size-fits-all approach, increasing attention to sex differences in PA-related risks and benefits could augment precision medicine efforts to improve health outcomes for all.

13. **Female Sex and Low Flow: A Double Paradox in Aortic Stenosis?***

Introduction

As the treatment of aortic stenosis (AS) continues to evolve with expanding indications to a broader subset of patients, reduction in procedural risk, advances in valve design, and improved hemodynamics, it is of increasing importance that patients are selected for the right intervention for each specific subpopulation. Such subsets include low flow-low gradient, female population, multivalvular disease, and those with concomitant multivessel atherosclerotic disease among many other conditions. The approach to

intervention in women with AS has been of particular interest for a variety of reasons. There are historically well-described differences in annuli size and hemodynamics among other features between men and women with women typically having smaller annuli on average than men. However, the sex-related issues in AS therapy are not just related to size. Women also have different left ventricular (LV) responses to AS and are known to have a higher prevalence of heart failure with preserved ejection fraction and paradoxical low flow-low gradient (PLF LG) AS. Sex-based disparities in AS care for women are also apparent, where women are less often referred for AS intervention.

It is the intersection of sex and flow status that is assessed in the study by Carter-Storch et al[1] in this issue of JACC: Advances who analyzed data from the PARTNER 2 and 3 trials to assess the impact of PLF on adverse outcomes after transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR).[1]

Two-year occurrence of the composite of death or heart failure hospitalization (primary endpoint) and of all-cause mortality alone (secondary endpoint) were analyzed. Out of just over 2,000 patients, PLF was present in 390 men and 239 women (30 vs 26%, P = 0.06). PLF was associated with a higher rate of NYHA functional class III to IV dyspnea and a higher prevalence of atrial fibrillation. PLF was a significant predictor of the primary endpoint among women undergoing SAVR in multivariate analysis but was not associated with a worse outcome in any of the other groups that were studied according to sex or intervention. They conclude that in women with PLF, TAVR may be more appropriate compared to SAVR.

The authors have highlighted that sex in conjunction with PLF LG AS is an important consideration when assessing patients for TAVR vs SAVR. The intersection of these 2 subsets of AS patients is notable considering the unique considerations for AS intervention in women, and those patients with PLF LG or normal flow AS are at increased risk of mortality.[2] As TAVR continues to progress as the predominant mode of intervention for AS across all risk spectrums and is generally associated with low risk, the field of

structural interventions pushes our understanding of tailoring therapy to each individual vs a “one size fits all” approach. Unlike many other fields in cardiovascular medicine, women have, relatively speaking, had a higher representation in TAVR studies compared to other cardiovascular studies. However, representation of women in such studies in and of itself is not sufficient, as the question of how sex factors into the discussion of appropriate mode of intervention is still in question. There are definitive anatomic differences between men and women, as mentioned earlier, as well as differences in left ventricular response to AS and outcomes after intervention. Valvular pathology is also different leading to differences in calcium score for men and women when evaluating AS severity, where the recommended cut-off valve for significant calcification is significantly less in women than in men.[3] The issue of reference points such as valve calcification and differences in adaptive response is also important to consider. LV hypertrophy tends to be more concentric in women with predominant fibrosis and is associated with diastolic dysfunction,[4,5] and women tend to also have smaller valve areas and lower gradients. As is examined in this study, analysis of the PLF LG population has historically relied on cutoffs of stroke volume index <35 ml/m^2 as the definition of low flow. Considering smaller LV cavities and annuli, PLF has been noted more frequently in women, but whether this dichotomous cutoff of stroke volume index is as predictive in women vs men is unclear and thus begs the question of whether such traditional cutoffs are appropriate for men and women comparatively.

The results found in this study and many others in regard to female sex and AS interventions continue to highlight the need for not only more data on women in this area but also tailored interventions. Early data from PARTNER I suggested a paradox that female sex is an adverse predictor of outcomes after SAVR with favorable outcomes in TAVR in high-risk patients despite a higher risk of vascular complications. However, subsequent data analyzed in mixed populations of intermediate and lower risk cohorts have been discordant in regards to outcomes after TAVR vs SAVR in women.[6-10] A meta-analysis from 2018 with nearly 50% women noted increased vascular

complications but greater 1-year survival.[11] The continued surge of transcatheter aortic interventions only furthers the need to dedicate studies of AS intervention in women to specifically account for sex-specific factors such as low flow and small annuli. The recent VIVA study compared hemodynamic and clinical outcomes between TAVR and SAVR in patients with severe AS and small aortic annuli. The study population included 93% women with no differences between TAVR and SAVR in regard to prosthesis patient prosthesis mismatch and no differences in stroke or mortality at 30 days and 2 years.[12] Findings such as these also strengthen the need for such dedicated studies as WIN-TAVI, which is an international, multicenter, prospective, observational registry of women undergoing TAVR across multiple sites, mostly in Europe. Initial analysis from WIN-TAVI noted that in intermediate to high-risk women, TAVR was associated with low risk of 1-year mortality and stroke.[13] This registry is also unique in that reproductive history was collected as a variable, which historically has not been included in large-scale registry analyses. Further studies such as the RHEIA (Randomized Research in Women All Comers With Aortic Stenosis) trial are currently ongoing to assess TAVR compared to SAVR in symptomatic women.[14] Women are not just "smaller" versions of men, and progressive research in AS interventions will continue to help guide clinicians in the care of this particular subset of patients.

14. Effect of Sex and Flow Status on Outcomes After Surgical or Transcatheter Aortic Valve Replacement

Background

Low stroke volume index <35 ml/m^2 despite preserved ejection fraction (paradoxical low flow [PLF]) is associated with adverse outcomes in patients with aortic stenosis undergoing transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR). However, whether the risk associated with PLF is similar in both sexes is unknown.

Objectives

The purpose of this study was to analyze the risk associated with PLF in severe aortic stenosis for men and women randomized to TAVR or SAVR.

Methods

Patients with ejection fraction ≥50% from the PARTNER (The Placement of Aortic Transcatheter Valves) 2 and 3 trials were stratified by sex and treatment arm. The impact of PLF on the 2-year occurrence of the composite of death or heart failure hospitalization (primary endpoint) and of all-cause mortality alone (secondary end point) was analyzed. Analysis of variance was used to assess baseline differences between groups. Multivariate Cox regression analysis was used to identify predictors of the endpoint.

Results

Out of 2,242 patients, PLF was present in 390 men and 239 women (30% vs 26%, P = 0.06). PLF was associated with a higher rate of NYHA functional class III to IV dyspnea (60% vs 54%, P < 0.001) and a higher prevalence of atrial fibrillation (39% vs 24%, P < 0.001). PLF was a significant predictor of the primary endpoint among women undergoing SAVR in multivariate analysis (adjusted HR: 2.25 [95% CI: 1.14-4.43], P = 0.02) but was not associated with a worse outcome in any of the other groups (all P > 0.05).

Conclusions

In women with PLF, TAVR may improve outcomes compared to SAVR. PLF appears to have less impact on outcomes in men.

Introduction

Since the inception of transcatheter aortic valve replacement (TAVR) 30 years ago,[1] it has proven to be a noninferior or superior alternative to surgical aortic valve replacement (SAVR) among patients with severe aortic stenosis (AS). Although short- and medium-term outcomes are comparable between the 2 treatment modalities for patients at low and intermediate risk,[2,3] long-term outcomes for TAVR are still uncertain, and TAVR is therefore primarily used

in patients with shorter life expectancy or intermediate/high surgical risk, after individual heart team evaluation.[4,5]

Although AS was previously thought to be similar in men and women, several sex-specific studies have shown that there are differences between the sexes in pathophysiology, epidemiology, presentation of AS, and outcome after aortic valve replacement (AVR).[6] Among high-risk patients in the PARTNER (The Placement of Aortic Transcatheter Valves) 1 trial, women had significantly reduced 2-year survival with SAVR compared to TAVR.[7] Whether this applies to low- and intermediate-risk patients is unknown, but in an analysis of the PARTNER 2, SAPIEN 3 cohort of high- and intermediate-risk patients, neither the combined nor individual risk cohorts showed sex differences in mortality or disabling stroke out to 1 year.[8] Moreover, patients with AS often present with a low flow state, defined as a stroke volume index (SVi) <35 ml/m^2, either with reduced (classical low flow) or preserved (paradoxical low flow [PLF]) left ventricular (LV) ejection fraction (LVEF). PLF has been shown to be associated with increased mortality compared to patients with normal flow (NF) after AVR.[9-11] PLF is usually more prevalent among women,[10,12] but whether the prognostic implication of PLF is the same in men vs women after AVR is unknown.

The aim of this study was, therefore, to investigate the prognostic implication of PLF among men and women after TAVR and SAVR among patients with low and intermediate surgical risk enrolled in the PARTNER 2 and 3 trials.

Methods

Study sample

The PARTNER 2 and 3 trials were multicenter, randomized clinical trials comparing TAVR and SAVR among patients with intermediate operative risk (PARTNER 2: Society of Thoracic Surgeons score 4-8%)[2] and low operative risk (PARTNER 3: Society of Thoracic Surgeons score <4%).[3] All patients had severe AS, with aortic valve area (AVA) ≤0.8 or 1.0 cm^2 in the 2 trials, respectively, and mean gradient ≥40 mm Hg. Patients in PARTNER 2 were

randomly assigned to SAVR with any commercially available bioprosthetic surgical valve or TAVR with an Edwards SAPIEN XT, in PARTNER 3 to SAVR with any commercially available bioprosthetic surgical valve or TAVR with an Edwards SAPIEN 3 transcatheter heart valve. Full lists of inclusion and exclusion criteria have been previously published.[2,3] The PARTNER trials were approved by the Institutional Review Board at each site, and written informed consent was obtained from all the patients.

In the present analysis, we excluded patients with reduced LVEF <50%, as well as patients with missing data for AVA, SVi, mean gradient, or LVEF.

Echocardiography

Echocardiograms were analyzed at a core laboratory blinded to randomization and clinical endpoints, as previously described.[13] LV dimensions and mass, as well as biplane Simpson LVEF, were estimated as recommended by the American Society of Echocardiography guidelines for chamber quantification.[14] Peak aortic jet velocity was measured at the window of maximal velocity, and mean gradient was estimated using the simplified Bernoulli equation. Stroke volume was calculated by multiplying the LV outflow tract diameter and Doppler velocity time integral measured just proximal to the native annulus. AVA was calculated from the continuity equation and indexed to body surface area (AVAi).[15] Valvular regurgitations at baseline were assessed and graded as recommended by the American Society of Echocardiography.[16] Patients were dichotomized according to guidelines as NF: SVi ≥35 ml/m^2 or PLF: SVi <35 ml/m^2.[5]

Patient-prosthesis mismatch (PPM) was defined using the normal reference value of AVA (for the model and size of the implanted prosthesis) indexed to the patient's body surface area, with thresholds adjusted for obese patients as per guidelines.[17]

Postoperative echocardiograms performed 1 month after AVR were analyzed for the presence of transvalvular or paravalvular regurgitation and graded

according to American Society of Echocardiography guidelines.[16] Mean gradient, maximal jet velocity, and AVA were also measured at 1 month.

Procedure

Details on the procedure for implantation of the Edwards SAPIEN XT[18] and the SAPIEN 3[19] TAVR systems have been previously published. Procedures were performed via transfemoral or alternative access, depending on preprocedural assessment. Dual antiplatelet therapy with clopidogrel and aspirin was recommended for at least 1 month after TAVR.

Study endpoints

The primary endpoint in this substudy was the composite of death from any cause or rehospitalization for heart failure symptoms within 2 years. The secondary endpoint was all-cause mortality within 2 years. Time to event was defined as the time to the first endpoint within 2 years; for censored cases, time to event was either the time to the last participation date, or 730 days, whichever was shorter. A clinical events committee independently adjudicated all potential events. Clinical outcomes were reported as defined by the Valve Academic Research Consortium-2 definitions.[20]

Statistics

Analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables were used to compare patient demographics, procedure information, and echo parameters among ≥3 groups; Student's t-test and chi-square test were used to compare continuous variables and categorical variables, respectively, between 2 groups. Kaplan-Meier curves and log-rank tests were used to compare the primary and secondary endpoints by treatment and SVi group within each sex. Multivariable Cox regression models were used to further identify predictors of endpoints from among the following covariates: SVi, age, sex, coronary artery disease, NYHA functional class, hypertension, diabetes, atrial fibrillation, chronic obstructive

pulmonary disease, chronic kidney disease, treatment arm (SAVR/TAVR), LVEF, mean gradient, patient-prosthesis mismatch, and transvalvular

Table 1Clinical and Echocardiographic Characteristics According to Sex and Flow Profile

		Men (N = 1,321)			Women (N = 921)			
	Total (N = 2,242)	**SVi <35 (n = 390)**	**SVi ≥35 (n = 931)**	**Within Men P Value**	**SVi <35 (n = 239)**	**SVi ≥35 (n = 682)**	**Within Women P Value**	**ANOVA P Value**
Clinical parameters								
Age (y)	78.9 ± 7.5	78.4 ± 7.9	78.3 ± 7.5	0.8572	79.6 ± 7.2	79.9 ± 7.1	0.5706	<0.0001
Body mass index (kg/m^2)	29.4 ± 5.9	30.5 ± 5.5	28.8 ± 4.8	<0.0001	31.1 ± 7.4	29.0 ± 6.7	<0.0001	<0.0001
Body surface area (m^2)	1.9 ± 0.2	2.1 ± 0.2	2.0 ± 0.2	<0.0001	1.8 ± 0.2	1.8 ± 0.2	<0.0001	<0.0001
STS score (%)	4.2 (2.2, 5.6)	4.2 (2.2, 5.6)	3.4 (1.7, 5.1)	<0.0001	4.7 (3.4, 6.3)	4.7 (2.7, 6.1)	0.4457	<0.0001
NYHA functional class I	8 (0.4%)	1 (0.3%)	5 (0.5%)	0.0437	0 (0.0%)	2 (0.3%)	0.0195	<0.0001
NYHA functional class II	1,008 (45.0%)	169 (43.3%)	471 (50.6%)		79 (33.1%)	289 (42.4%)		

Table 1Clinical and Echocardiographic Characteristics According to Sex and Flow Profile

		Men (N = 1,321)			Women (N = 921)			
	Total (N = 2,242)	**SVi <35 (n = 390)**	**SVi ≥35 (n = 931)**	**Within Men P Value**	**SVi <35 (n = 239)**	**SVi ≥35 (n = 682)**	**Within Women P Value**	**ANOVA P Value**
NYHA functional class III	1,024 (45.7%)	177 (45.4%)	382 (41.1%)		129 (54.0%)	336 (49.3%)		
NYHA functional class IV	201 (9.0%)	43 (11.0%)	72 (7.7%)		31 (13.0%)	55 (8.1%)		
KCCQ overall summary score	62.5 (44.8, 80.0)	61.1 (43.2, 76.8)	68.0 (51.0, 84.7)	<0.0001	53.4 (37.8, 70.4)	58.7 (42.7, 77.0)	0.0104	<0.0001
Diabetes mellitus	715 (31.9%)	162 (41.5%)	290 (31.1%)	0.0003	82 (34.3%)	181 (26.6%)	0.0229	<0.0001
Coronary artery disease	1,147 (51.2%)	239 (61.3%)	529 (56.9%)	0.1448	107 (44.8%)	272 (39.9%)	0.1864	<0.0001
Atrial fibrillation	626 (27.9%)	169 (43.3%)	246 (26.5%)	<0.0001	74 (31.0%)	137 (20.1%)	0.0006	<0.0001
Chronic obstructive pulmonary disease	452 (20.2%)	99 (25.4%)	180 (19.4%)	0.0155	44 (18.4%)	129 (19.0%)	0.8341	0.048

Table 1Clinical and Echocardiographic Characteristics According to Sex and Flow Profile

	Men (N = 1,321)				Women (N = 921)			
	Total (N = 2,242)	**SVi <35 (n = 390)**	**SVi ≥35 (n = 931)**	**Within Men P Value**	**SVi <35 (n = 239)**	**SVi ≥35 (n = 682)**	**Within Women P Value**	**ANOVA P Value**
Creatinine >2 mg/dL	83 (3.7%)	11 (2.8%)	42 (4.5%)	0.1532	7 (2.9%)	23 (3.4%)	0.7396	0.37
Frailty	80 (3.6%)	8 (2.1%)	22 (2.4%)	0.7334	13 (5.4%)	37 (5.4%)	0.9971	0.001
AV hemodynamics								
AV mean gradient (mm Hg)	47.4 ± 12.3	44.2 ± 10.6	48.3 ± 12.0	<0.0001	45.8 ± 13.1	48.7 ± 12.8	0.0026	<0.0001
AV peak jet (cm/s)	442.0 ± 52.8	426.3 ± 46.8	445.9 ± 50.9	<0.0001	434.4 ± 56.9	448.3 ± 55.1	0.0009	<0.0001
AV area index (cm^2/m^2)	0.4 ± 0.1	0.3 ± 0.1	0.4 ± 0.1	<0.0001	0.3 ± 0.1	0.4 ± 0.1	<0.0001	<0.0001
LV systolic structure and function								
SVi (mL/m^2)	40.3 ± 8.7	30.7 ± 3.4	43.9 ± 7.2	<0.0001	30.7 ± 3.23	44.3 ± 7.0	<0.0001	<0.0001
Heart rate	68 ± 12	72 ± 13	64 ± 10	<0.0001	77 ± 12	69 ± 11	<0.0001	<0.0001
LV ejection fraction (%)	64.0 ± 7.3	61.6 ± 6.9	64.1 ± 6.9	<0.0001	62.9 ± 7.8	65.6 ± 7.4	<0.0001	<0.0001

Table 1Clinical and Echocardiographic Characteristics According to Sex and Flow Profile

		Men (N = 1,321)			Women (N = 921)			
	Total (N = 2,242)	**SVi <35 (n = 390)**	**SVi ≥35 (n = 931)**	**Within Men P Value**	**SVi <35 (n = 239)**	**SVi ≥35 (n = 682)**	**Within Women P Value**	**ANOVA P Value**
LV end-diastolic diameter (mm)	4.7 ± 0.6	4.8 ± 0.5	5.0 ± 0.5	<0.0001	4.3 ± 0.5	4.5 ± 0.5	0.0003	<0.0001
LV end-systolic diameter (mm)	3.0 ± 0.6	3.1 ± 0.6	3.1 ± 0.6	0.1883	2.8 ± 0.6	2.7 ± 0.5	0.5329	<0.0001
LV end-diastolic volume (mL)	99.8 ± 28.9	103.6 ± 25.7	113.4 ± 28.9	<0.0001	76.9 ± 20.1	85.9 ± 21.2	<0.0001	<0.0001
LV end-systolic volume (mL)	35.7 ± 14.2	39.5 ± 13.4	40.5 ± 14.9	0.2628	28.2 ± 10.9	29.0 ± 10.6	0.3202	<0.0001
LV mass index (g/m^2)	198.8 ± 108.2	203.7 ± 106.2	201.6 ± 118.2	0.7715	193.2 ± 98.3	194.1 ± 97.5	0.9080	0.3804
Relative wall thickness	0.5 (0.4-0.5)	0.5 (0.4-0.5)	0.4 (0.4-0.5)	<0.0001	0.5 (0.4-0.6)	0.5 (0.4-0.5)	0.0002	<0.0001
Concomitant valve regurgitations								

Table 1Clinical and Echocardiographic Characteristics According to Sex and Flow Profile

	Men (N = 1,321)				Women (N = 921)			
	Total (N = 2,242)	**SVi <35 (n = 390)**	**SVi ≥35 (n = 931)**	**Within Men P Value**	**SVi <35 (n = 239)**	**SVi ≥35 (n = 682)**	**Within Women P Value**	**ANOVA P Value**
Moderate + mitral regurgitation	154 (7.0%)	25 (6.7%)	46 (5.0%)	0.2420	25 (10.8%)	58 (8.7%)	0.3424	0.004
Moderate + aortic regurgitation	149 (6.7%)	11 (2.9%)	73 (7.9%)	0.0007	7 (3.0%)	58 (8.6%)	0.0042	0.0002
Moderate + tricuspid regurgitation	155 (7.3%)	27 (7.5%)	47 (5.3%)	0.1202	30 (13.3%)	51 (7.8%)	0.0138	0.0004

regurgitation at 30 days.

All statistical analyses were done using SAS version 9.4 (SAS institute). A 2-sided P value <0.05 was considered statistically significant.

Results

Out of a total of 2,953 patients (PARTNER 2 SAVR: n = 936, PARTNER 2 TAVR: n = 1,069, PARTNER 3: 948), 711 patients were excluded due to LVEF <50% or missing echo data. Of the 2,242 patients remaining in this study, 1,321 (59%) were men and 921 (41%) were women. There were 629 patients (28%) with PLF, with a numerically higher proportion of PLF among men than women (30% vs 26%, P = 0.06).

Baseline characteristics according to sex and flow

Women in this study, compared with men, were older, and had higher NYHA functional class and lower Kansas City Cardiomyopathy Questionnaire score at baseline. They had lower prevalence of coronary artery disease, diabetes, and atrial fibrillation, but more often had chronic kidney disease and frailty indicators. On echocardiography, women's SVi and AVAi were similar to that of men. Women had higher LVEF, but a higher prevalence of ≥ moderate mitral and tricuspid regurgitation (**Table 1**, **Supplemental Table 1**).

Values are mean ± SD, median (Q1, Q3), or n (%). ANOVA was used for continuous variables. Chi-square tests were used for categorical variables. An expanded table is presented as in **Supplemental Table 3**.

AV = aortic valve; KCCQ = Kansas City Cardiomyopathy Questionnaire; LV = left ventricular; NYHA = New York Heart Association Class dyspnea symptoms; STS = Society of Thoracic Surgeons; SVi = stroke volume index.

Compared to patients with NF, patients with PLF had a higher STS score, higher NYHA class, lower Kansas City Cardiomyopathy Questionnaire score, higher prevalence of coronary artery disease and diabetes mellitus, higher heart rate, and higher prevalence of pacemaker and atrial fibrillation (**Supplemental Table 2**). These findings were similar when flow was further stratified by sex (**Supplemental Table 3**). On preprocedural echocardiographic examination, patients with PLF also had lower AVAi, SVi, and transvalvular gradient, smaller LV dimensions and lower LVEF. This was especially the case among women with PLF, who had the smallest LV end-diastolic volumes. Patients with PLF had more mitral and tricuspid regurgitation, but had less aortic regurgitation (**Table 1**, **Supplemental Table 2.1**).

Procedural and postprocedural data

Procedural and postprocedural data according to sex and preprocedural SVi are presented in **Table 2** for SAVR and **Table 3** for TAVR. During both TAVR and SAVR, women received smaller sized valves than men. For SAVR patients, 22% of women and only 1% of the men received a valve size ≤19 mm. This

difference was even more pronounced in the subgroup of women with PLF (**Table 2**). For TAVR patients, similar findings were observed with 9.6% of women and <0.1% of men receiving a 20 mm valve size, and again women with PLF more often received smaller valves compared to women with NF (**Table 3**).

Values are n (%), median (Q1, Q3), or mean ± SD. ANOVA was used for continuous variables. Chi-square tests were used for categorical variables.

AV = aortic valve; ICU = intensive care unit; PPM = patient-prosthesis mismatch; SAVR = surgical aortic valve replacement; SVi = stroke volume index.

Table 3Procedural Information by Sex and SVi in TAVR Group

		Men (N = 590)			**Women (N = 487)**		
	Total (N = 1,218)	**SVi <35 (N = 509)**	**SVi ≥35 (n = 222)**	**Within Men P Value**	**SVi <35 (n = 372)**	**SVi ≥35 (n = 115)**	**Within Women P Va**
Approach							
Transfemoral	1,133 (93.0%)	204 (91.9%)	474 (93.1%)	0.8071	110 (95.7%)	345 (92.7%)	0.1837
Transapical	60 (4.9%)	13 (5.9%)	24 (4.7%)		2 (1.7%)	21 (5.6%)	
Other	25 (2.1%)	5 (2.3%)	11 (2.2%)		3 (2.6%)	6 (1.6%)	
Valve size							
20 mm	48 (3.9%)	0 (0.0%)	1 (0.2%)	0.0608	15 (13.0%)	32 (8.6%)	0.4549

Table 3Procedural Information by Sex and SVi in TAVR Group

	Men (N = 590)				Women (N = 487)			
	Total (N = 1,218)	**SVi <35 (N = 509)**	**SVi ≥35 (n = 222)**	**Within Men P Value**	**SVi <35 (n = 372)**	**SVi ≥35 (n = 115)**	**Within Women P Va**	
23 mm	417 (34.2%)	37 (16.7%)	54 (10.6%)		71 (61.7%)	255 (68.5%)		
26 mm	548 (45.0%)	134 (60.4%)	304 (59.7%)		28 (24.3%)	82 (22.0%)		
29 mm	205 (16.8%)	51 (23.0%)	150 (29.5%)		1 (0.9%)	3 (0.8%)		
Days in hospital	4.0 (3.0, 5.0)	3.0 (3.0, 5.0)	3.0 (3.0, 4.0)	0.7330	4.0 (3.0, 5.0)	4.0 (3.0, 6.0)	0.8521	
Days in ICU	2.0 (2.0, 3.0)	2.0 (2.0, 2.0)	2.0 (1.0, 3.0)	0.7779	2.0 (1.0, 3.0)	2.0 (2.0, 3.0)	0.8738	
Discharged to home?	1,089 (89.4%)	203 (91.4%)	477 (93.7%)	0.2676	97 (84.3%)	312 (83.9%)	0.9030	
30 d echo information								
AV mean gradient (mm Hg)	11.7 ± 4.7	10.9 ± 4.0	12.1 ± 4.9	0.0015	11.3 ± 4.2	13.3 ± 5.5	0.0005	
AV peak velocity (cm/s)	230.9 ± 43.0	222.4 ± 38.0	233.7 ± 41.6	0.0007	226.0 ± 41.6	242.8 ± 46.2	0.0006	
AV area (cm^2)	1.7 ± 0.4	1.7 ± 0.3	1.9 ± 0.3	<0.0001	1.5 ± 0.3	1.5 ± 0.3	0.1064	

Table 3Procedural Information by Sex and SVi in TAVR Group

		Men (N = 590)				Women (N = 487)			
	Total (N = 1,218)	**SVi <35 (N = 509)**	**SVi ≥35 (n = 222)**	**Within Men P Value**	**SVi <35 (n = 372)**	**SVi ≥35 (n = 115)**	**Within Women P Va**	
AV area index (cm^2/m^2)	0.9 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	<0.0001	0.8 ± 0.2	0.9 ± 0.2	0.0008	
PPM	724 (36.8%)	84 (41.0%)	124 (26.0%)	<0.0001	51 (47.2%)	103 (30.9%)	0.0020	

Values are n (%), median (Q1, Q3), or mean ± SD. ANOVA was used for continuous variables. Chi-square tests were used for categorical variables.

AV = aortic valve; ICU = intensive care unit; PPM = patient-prosthesis mismatch; SVi = stroke volume index; TAVR = transcatheter aortic valve replacement.

Women had longer hospital stays after the procedure and were less frequently discharged to their homes. The 30-day mortality rate for the whole sample was numerically higher without statistical significance among women with NF and PLF (2.2 and 2.5%) compared to men with NF and PLF (1.2 and 1.3%) (ANOVA P = 0.26).

At the 1-month echocardiogram, patients with PLF had smaller AVAi despite lower mean gradients, and more often had patient-prosthesis mismatch (**Tables 2** and **3**). This was most pronounced for women with PLF undergoing SAVR, where 63 (62%) had patient-prosthesis mismatch (**Table 2**).

Association of PLF and sex with outcomes

During a median follow-up of 2 (IQR: 2-2) years, there were 180 deaths and 103 hospitalizations for heart failure.

In the whole sample, significant predictors of the primary endpoint were age, atrial fibrillation, chronic obstructive pulmonary disease, lower LVEF, and lower mean gradient prior to the procedure. In men, the same variables, except LVEF, were predictors of the endpoint, while in women atrial fibrillation was the only significant independent predictor (**Figure 1**).

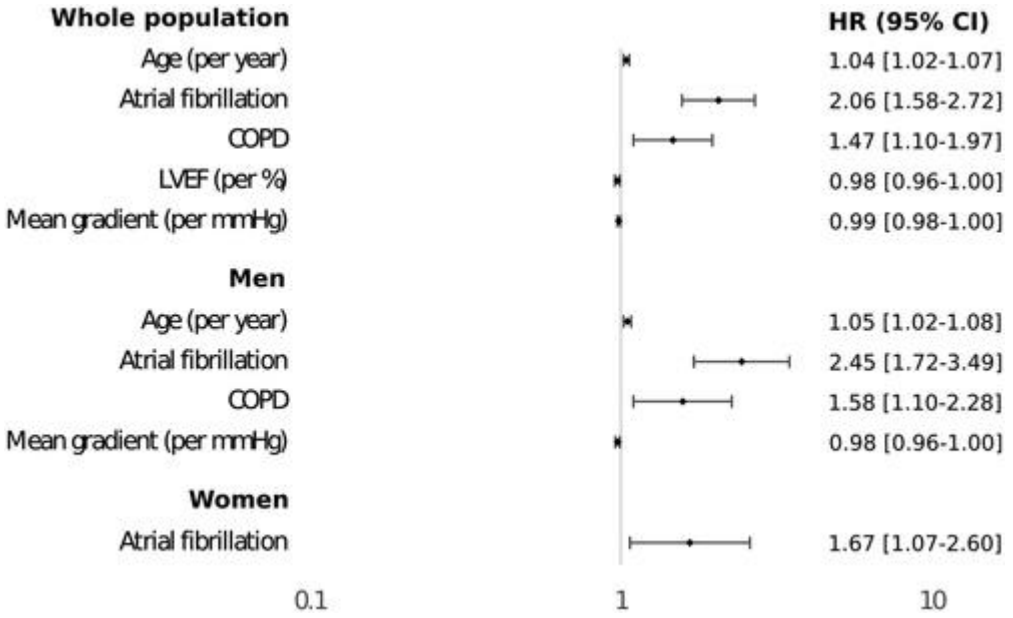


Figure 1

Forest Plot of Significant Multivariable Predictors of Death or Rehospitalization for Heart Failure in Whole Sample

Multivariable cox regression analysis. Variables are the only significant multivariable predictors of the combined primary endpoint. The following covariates were added in the model: Age, sex, coronary artery disease, NYHA functional class, hypertension, diabetes, atrial fibrillation, COPD, chronic kidney disease, treatment (SAVR/TAVR), LVEF, stroke volume index, mean gradient, patient-prosthesis mismatch, and transvalvular regurgitation at 30 days. The full multivariable analyses results are available as **Supplemental Tables 4 to 8**. COPD = chronic obstructive pulmonary disease; LVEF = left vventricular ejection fraction; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

Low preprocedural SVi was not a predictor of the primary endpoint in the whole cohort, in women or men separately, or in the subgroup of TAVR patients (**Supplemental Tables 5** and **6**). However, among patients randomized to SAVR, low SVi was associated with the primary outcome in women (univariable HR: 1.98 [95% CI: 1.09-3.62], P = 0.03) but not in men (HR: 1.20 [95% CI: 0.68-2.13], P = 0.40) (**Supplemental Tables 7** and **8**). Among women undergoing SAVR, after adjusting for known risk factors (age, coronary artery disease, NYHA functional class, hypertension, diabetes, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, LVEF, preprocedural mean gradient, patient-prosthesis mismatch, and transvalvular regurgitation at 30 days), PLF was the only independent predictor of the primary outcome (adjusted HR: 2.25 [95% CI: 1.14-4.43], P = 0.02) (**Table 4**, **Central Illustration**).

Table 4Multivariable Cox Model for Death/Heart Failure Hospitalization (Female SAVR Patients)

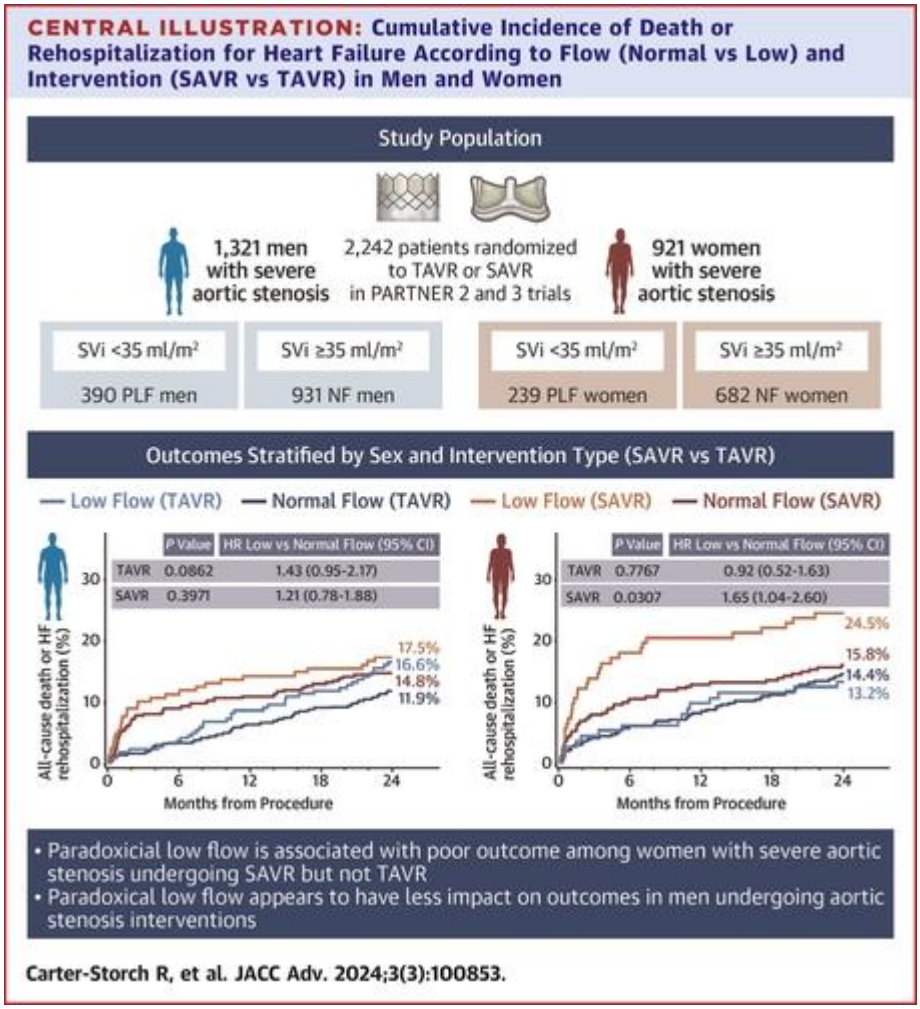
	HR (95% CI)	**P Value**
SVi <35 mL/m^2	2.25 (1.14-4.43)	0.02
Age, per 1 y increase	1.02 (0.96-1.08)	0.53
Coronary artery disease	1.05 (0.56-1.97)	0.88
NYHA functional class III/IV (dyspnea symptoms)	0.80 (0.39-1.63)	0.54
Hypertension	3.31 (0.45-24.51)	0.24
Diabetes	1.11 (0.56-2.22)	0.77

Table 4Multivariable Cox Model for Death/Heart Failure Hospitalization (Female SAVR Patients)

	HR (95% CI)	**P Value**
Atrial fibrillation	1.51 (0.76-2.96)	0.24
Chronic obstructive pulmonary disease	1.73 (0.80-3.75)	0.17
Chonic kidney disease moderately to severely decreased or poorer	0.73 (0.33-1.61)	0.43
LVEF, per 1% increase	0.96 (0.91-1.01)	0.14
Aortic mean gradient, per 1 mm Hg increase	1.01 (0.99-1.03)	0.40
Patient-prothesis mismatch	0.80 (0.40-1.61)	0.54
Transvalvular regurgitation at 30 d ≥ mild	2.86 (0.37-22.17)	0.31

30-day landmark multivariable Cox regression.

HF = heart failure; LVEF = left ventricular ejection fraction; SAVR = surgical aortic valve replacement; SVi = stroke volume index.



Central Illustration

Cumulative Incidence of Death or Rehospitalization for Heart Failure According to Flow (Normal vs Low) and Intervention (SAVR vs TAVR) in Men and Women

Multivariable logistic regression models: hazard rates are adjusted for age, coronary artery disease, NYHA functional class, hypertension, diabetes, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, left ventricular ejection fraction, preprocedural aortic valve mean gradient, postprocedural patient-prosthesis mismatch, and transvalvular regurgitation at 30 days. NF = normal flow; PLF = paradoxical low flow; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

Low preprocedural SVi was not a risk factor for 2-year all-cause mortality in the whole cohort, or in any of the 4 groups (according to sex and TAVR/SAVR)

(**Figure 2**). However, the 2-year mortality rate for women with PLF undergoing SAVR was higher compared to women with PLF undergoing TAVR (13.9% vs 6.2%, univariable HR 2.42 [95% CI: 1.00-5.84], P = 0.049). When adjusting for known risk factors (age, coronary artery disease, hypertension, diabetes, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease ≥ moderate-severe, LVEF, mean gradient), this difference was no longer significant, but there was a nonsignificant trend toward higher risk of all-cause mortality in women with PLF undergoing SAVR compared to those undergoing TAVR (adjusted HR: 2.33 [95% CI: 0.91-5.98], P = 0.08).

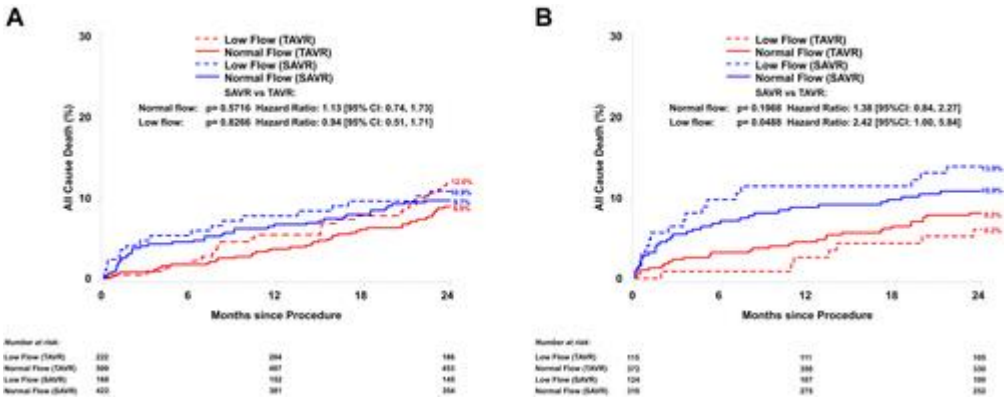


Figure 2

Cumulative Incidence of Mortality

Cumulative incidence of death according to flow (normal vs low) and intervention (SAVR vs TAVR) in men (A) and women (B). Multivariate logistic regression models: hazard rates are adjusted for age, coronary artery disease, NYHA functional class, hypertension, diabetes, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, left ventricular ejection fraction, preprocedural aortic valve mean gradient, postprocedural patient-prosthesis mismatch, and transvalvular regurgitation at 30 days. SAVR = surgical aortic valve replacement; TAVR = ttranscatheter aortic valve replacement.

Discussion

This analysis of data from the PARTNER 2 and 3 trials represents one of the largest studies on the impact of sex and preprocedural flow status on outcomes following SAVR and TAVR. Our main findings are that in patients with severe AS and preserved LVEF: 1) PLF was a risk factor for death or heart failure hospitalization among women undergoing SAVR but not TAVR; 2) women with PLF had a trend toward increased risk of all-cause mortality with SAVR compared with TAVR; and 3) PLF was not associated with worse outcomes among men undergoing either SAVR or TAVR.

Reduced SVi is a well-described risk factor for adverse outcomes in AS in observational studies,[12,21-25] although this association is attenuated in multivariable adjustment due to differences in comorbidities.[12,25] The increased risk of events is, in part, related to adverse LV remodeling with higher relative wall thickness,[9,10,24] more advanced diastolic dysfunction,[24,26] and a higher proportion of patients with atrial fibrillation.[13,22,27] Previous studies have mostly focused on PLF or sex as 2 isolated risk factors, whereas in our study, we show that the impact of PLF is not uniform among men and women: that is, TAVR appears to be superior to SAVR in the vulnerable subset of women with PLF, whereas women with NF or men (regardless of flow status) have similar outcomes with SAVR and TAVR. This finding is consistent with a previous study showing that PLF is an independent risk factor for long-term mortality after SAVR, but that this risk factor was only present in women or more prevalent in women.[9] It highlights the need to stratify AS studies according to sex, because of sex-specific differences in pathophysiology and prognosis.

The PLF group in this study had a higher proportion of diabetes, atrial fibrillation, and worse baseline symptom severity compared to the NF group, all of which are risk factors for worse prognosis after AVR;[10,13] these factors may explain, at least in part, the association between PLF and outcomes. However, after multivariable adjustment for known risk factors, PLF remained an independent risk factor among women undergoing SAVR.

The second interesting finding in this article was that among women with PLF, SAVR was associated with a higher 2-year mortality compared to TAVR. This should be interpreted with caution as the number of events in this subgroup was small, and because the association was no longer significant after multivariable adjustment. According to current guidelines from the American College of Cardiology/American Heart Association, both SAVR and transfemoral TAVR can be considered equal treatments and the choice depends on expected longevity of the patient and valve durability.[4] The guidelines do not take into consideration sex and flow status in the decision process for the management of patients with AS. However, based on our study, PLF could tip the decision in favor of TAVR compared with SAVR for women.

Other studies have found PLF to be a risk factor for worse outcomes after AVR.[9-11,13,27] In PLF patients in the PARTNER 1 trial, SAVR resulted in an early increased hazard compared to TAVR, though long-term survival was similar.[11] This early increase in mortality and in-hospital complications among PLF patients was confirmed in another observational study of patients undergoing SAVR, where known risk scores underestimated the perioperative risk in this group.[10] Part of the increased surgical risk associated with PLF may be attributable to concomitant risk factors, explaining why the association between PLF and increased long-term mortality after SAVR was no longer significant after multivariable adjustment.[10]

Among AS cohorts, women have worse prognosis than men, in part because they are less likely to be referred to AVR or they are referred later in the course of the disease.[28-30] Furthermore, women have higher 30-day mortality and higher in-hospital complication rates after SAVR than men, even after propensity score matching.[29,31] Several factors may contribute to this increased risk in women vs men. In the present study, the prevalence of frailty was higher in women than in men. Frailty has been reported as an independent predictor of outcome after AVR.[32,33] The LV remodeling process in women with AS also differs from that in men, with more pronounced LV concentric remodeling and higher extent of diffuse myocardial fibrosis, as was

also seen in our sample, where women with PLF had the smallest LV volumes.[34-36]

Women also have smaller aortic annuli than men,[12,37,38] increasing their risk for prosthesis-patient mismatch, which may hinder the reverse LV remodeling process, regression of LV diastolic dysfunction, and thus prognosis following AVR.[39,40] This issue may be more important with SAVR than TAVR, because of the higher risk of severe prosthesis-patient mismatch associated with SAVR in patients with a small annulus.[40,41] In the SAVR arm of the present study, women, especially women with PLF, received smaller valves than men, and they had the lowest AVA, indexed AVA, and the highest proportion of PPM at 1 month. Better effective orifice areas, lower postoperative gradients, and lower incidence of PPM achieved with TAVR may explain, at least in part, the better prognosis associated with TAVR vs SAVR in women.

Strengths and limitations

By combining data from the PARTNER 2 and 3 studies, we were able to perform one of the largest studies on preprocedural PLF in patients randomized to SAVR or TAVR. Previous studies have mostly been performed on retrospective data with the risk of residual confounding despite multivariable adjustment. Nevertheless, there are some limitations to this study. The first is that enrolled patients had to fulfill the inclusion criteria for the randomized trials, and thus our results may not be generalizable to all patients with AS.

We excluded patients with LVEF <50% and our conclusions can therefore not be extrapolated to patients with classical low flow. Furthermore, in the PARTNER 2 and 3 trials, patients with mean gradient <40 mmHg measured at rest at the recruitment sites were excluded, and our cohort therefore mostly consists of patients with low flow, high gradient AS. Although a number of patients with mean gradient <40 mmHg measured by the core lab are present, the sickest PLF patients (ie, the patients with the lowest gradients) were not included in the PARTNER trials. However, as a significant proportion of

patients with PLF, low gradient according to core lab measurements are present in this study and given that the difference in outcomes should be more pronounced in sicker patients, we believe our results are applicable to all women with low flow and either high or low gradient. In men, the absence of difference could be debatable and different in patients with more pronounced low gradient. Also, we did not test the possibility of sex-specific SVi thresholds[9] to define low flow, due to the number of studied groups.

We were only able to include 2-year outcomes, so long-term outcomes are still unknown, and should be studied. Furthermore, patient-centered outcomes and functional outcomes were not analyzed, and could be a topic for further studies.

Finally, as mentioned previously, the number of deaths was low in the sample, especially when looking at smaller subgroups, and our results regarding higher mortality for SAVR vs TAVR for women with PLF should therefore be considered hypothesis generating.

Conclusions

In the PARTNER 2 and 3 trials, PLF pattern was associated with worse outcomes in women undergoing SAVR but not TAVR. Moreover, among women with PLF, SAVR may possibly be associated with higher rates of 2-year mortality compared to TAVR. In men undergoing either SAVR or TAVR, PLF was not associated with worse outcomes.

These findings suggest that even among patients with preserved LV function, sex and flow status should be taken into account in the decision-making process between TAVR vs SAVR and that TAVR may potentially be preferred over SAVR in women with PLF. Further randomized studies are needed to confirm the superiority of TAVR over SAVR in this particular subset of patients.