

## **News in June 2023**

### **1. Sex-Related Differences in Patient Characteristics, Hemodynamics, and Outcomes of Cardiogenic Shock: INOVA-SHOCK Registry**

#### Background

Little is known about sex-related differences in outcomes of patients with cardiogenic shock (CS) treated within a standardized team-based approach (STBA).

#### Methods

We evaluated 520 consecutive patients (151 women; 369 men) with CS because of acute myocardial infarction (AMI) and heart failure (HF) in a single-center registry (January 2017–December 2019) and examined outcomes according to sex and CS phenotype. The primary outcome was in-hospital mortality. Secondary outcomes included major adverse cardiac events, 30-day mortality, major bleeding, vascular complications, and stroke.

#### Results

Women with AMI-CS had higher baseline acuity (CardShock score: female [F]: 5.5 vs male [M]: 4.0,  $P = .04$ ). Women with HF-CS more often presented with cardiac arrest (F: 12.4% vs M: 2.4%,  $P < .01$ ) and had higher rates of vasopressor use (F: 70.8% vs M: 58.0%,  $P = .04$ ) and mechanical circulatory support (F: 46.1% vs M: 32.5%,  $P = .04$ ). There were no sex-related differences in in-hospital mortality for AMI-CS (F: 45.2% vs M: 36.9%,  $P = .28$ ) and HF-CS (F: 28.1% vs M: 24.5%,  $P = .56$ ). Women with HF-CS experienced higher rates of major bleeding (F: 25.8% vs M: 13.7%,  $P = .02$ ) and vascular complications (F: 15.7% vs M:

6.1%,  $P = .01$ ); however, the F sex was not an independent predictor of these complications. No sex differences in survival were noted at 1 year.

## Conclusions

Within an STBA, although women with AMI-CS and HF-CS presented with higher acuity, they experienced similar in-hospital mortality, major adverse cardiac events, 30-day mortality, stroke, and 30-day readmissions as men. Further research is needed to understand better the extent to which historical differences in CS outcomes can be mitigated by an STBA.

## **2. Sex- and Age-Specific Interactions of Coronary Atherosclerotic Plaque Onset and Prognosis From CCTA**

### AIMS

The totality of atherosclerotic plaque derived from coronary computed tomography angiography (CCTA) emerges as a comprehensive measure to assess the intensity of medical treatment that patients need. This study examines the differences in age onset and prognostic significance of atherosclerotic plaque burden between sexes.

### METHODS AND RESULTS

From a large multi-center CCTA registry the Leiden CCTA score was calculated in 24 950 individuals. A total of 11 678 women ( $58.5 \pm 12.4$  years) and 13 272 men ( $55.6 \pm 12.5$  years) were followed for 3.7 years for major adverse cardiovascular events (MACE) (death or myocardial infarction). The age where the median risk score was above zero was 12 years higher in women vs. men (64-68 years vs. 52-56 years, respectively,  $P < 0.001$ ). The Leiden CCTA risk score was independently associated with MACE: score 6-20: HR 2.29 (1.69-3.10); score  $> 20$ : HR 6.71 (4.36-10.32) in women, and score 6-20: HR 1.64 (1.29-2.08); score

> 20: HR 2.38 (1.73-3.29) in men. The risk was significantly higher for women within the highest score group (adjusted P-interaction = 0.003). In premenopausal women, the risk score was equally predictive and comparable with men. In post-menopausal women, the prognostic value was higher for women [score 6-20: HR 2.21 (1.57-3.11); score > 20: HR 6.11 (3.84-9.70) in women; score 6-20: HR 1.57 (1.19-2.09); score > 20: HR 2.25 (1.58-3.22) in men], with a significant interaction for the highest risk group (adjusted P-interaction = 0.004).

## CONCLUSION

Women developed coronary atherosclerosis approximately 12 years later than men. Post-menopausal women within the highest atherosclerotic burden group were at significantly higher risk for MACE than their male counterparts, which may have implications for the medical treatment intensity.

### **3. Menstrual Cycle Length Linked to Cardiovascular Disease Outcomes**

Long and short menstrual cycle length is associated with increased risks for cardiovascular disease (CVD) and atrial fibrillation, according to a study published online May 24 in the *Journal of the American Heart Association*.

Chensihan Huang, M.D., from Nanfang Hospital in Guangzhou, China, and colleagues examined whether menstrual cycle characteristics are associated with cardiovascular outcomes in a study involving 58,056 women who had no CVD at baseline.

A total of 1,623 incident CVD cases were documented during a median 11.8 years of follow-up. The researchers found that for women with irregular cycles versus those with regular cycles, the hazard ratios were 1.19 (95 percent confidence interval, 1.07 to 1.31) for CVD events and 1.40 (1.14 to 1.72) for atrial fibrillation. The multivariable-adjusted hazard ratios were 1.29 (1.11 to 1.50) and 1.11 (0.98 to 1.56) for CVD events in association with short ( $\leq 21$  days) or long (35 days) menstrual cycles, respectively. Long and short cycle length was also associated with an increased risk for atrial fibrillation (hazard ratios, 1.30

[1.01 to 1.66] and 1.38 [1.02 to 1.87], respectively), while short cycle length was associated with an increased risk for coronary heart disease and myocardial infarction. No significant associations were seen for stroke and heart failure.

"These findings point out that women with menstrual cycle dysfunction might have adverse health consequences, and highlight the importance of monitoring menstrual cycle characteristics throughout women's reproductive life in the prevention of CVD and atrial fibrillation among women," the authors write.

#### **4. Sex-Specific Analysis of Rapid Up-Titration of GDMT After Hospitalisation for Acute Heart Failure**

AIMS

The aim of this study was to evaluate efficacy and safety of rapid up-titration of guideline directed medical therapies in men and women hospitalized for acute heart failure (AHF).

#### **METHODS AND RESULTS**

In STRONG-HF AHF patients were randomised just prior to discharge to either usual care (UC) or a high-intensity care (HIC) strategy of guideline-directed medical therapies (GDMT) up-titration. In these analyses, we compare the implementation, efficacy, and safety of the HIC strategy between men and women. In the randomised AHF population, 416/1078 (39%) were women. By day 90, a higher proportion of both sexes in the HIC group had been up-titrated to full doses of GDMT compared to UC. Overall, there were no differences in the primary endpoint between the sexes. The primary endpoint, 180-day HF readmission or death, occurred in 15.8% HIC women vs 23.5% women in the UC group (adjusted HR 0.67 [95% CI 0.40-1.13]) and in 14.9% HIC men vs 23.5% UC men (adjusted HR 0.57 [95% CI 0.38-0.88]), adjusted interaction  $p = 0.65$ . There was no significant treatment-by-sex interaction in quality-of-life improvement or in adverse events, including serious or fatal adverse events.

## CONCLUSION

The results of the current analyses suggest that a rapid up-titration of GDMT immediately after an AHF hospitalisation can and should be implemented similarly in men and women, as it results in reduction of 180-day all-cause death or HF readmission, quality-of-life improvement in both men and women with a similar safety profile.

## **5. Sex-Related Differences in Clinical Characteristics and Outcome Prediction Among Patients Undergoing Transcatheter Tricuspid Valve Intervention**

### BACKGROUND

Men and women differ regarding comorbidities, pathophysiology, and the progression of valvular heart diseases.

### OBJECTIVES

This study sought to assess sex-related differences regarding clinical characteristics and the outcome of patients with severe tricuspid regurgitation (TR) undergoing transcatheter tricuspid valve intervention (TTVI).

### METHODS

All 702 patients in this multicenter study underwent TTVI for severe TR. The primary outcome was 2-year all-cause mortality.

### RESULTS

Among 386 women and 316 men in this study, men were more often diagnosed with coronary artery disease (52.9% in men vs 35.5% in women;  $P = 5.6 \times 10^{-6}$ ). Subsequently, the underlying etiology for TR in men was predominantly secondary ventricular (64.6% in men vs 50.0% in women;  $P = 1.4 \times 10^{-4}$ ), whereas women more often presented with secondary atrial etiology (41.7% in women vs 24.4% in men,  $P = 2.0 \times 10^{-6}$ ). Notably, 2-year survival after TTVI was similar in

women and men (69.9% in women vs 63.7% in men;  $P = 0.144$ ). Multivariate regression analysis identified dyspnea expressed as New York Heart Association functional class, tricuspid annulus plane systolic excursion (TAPSE), and mean pulmonary artery pressure (mPAP) as independent predictors for 2-year mortality. The prognostic significance of TAPSE and mPAP differed between sexes. Consequently, we looked at right ventricular-pulmonary arterial coupling expressed as TAPSE/mPAP and identified sex-specific thresholds to best predict survival; women with a TAPSE/mPAP ratio  $<0.612$  mm/mm Hg displayed a 3.43-fold increased HR for 2-year mortality ( $P < 0.001$ ), whereas men with a TAPSE/mPAP ratio  $<0.434$  mm/mm Hg displayed a 2.05-fold increased HR for 2-year mortality ( $P = 0.001$ ).

## CONCLUSIONS

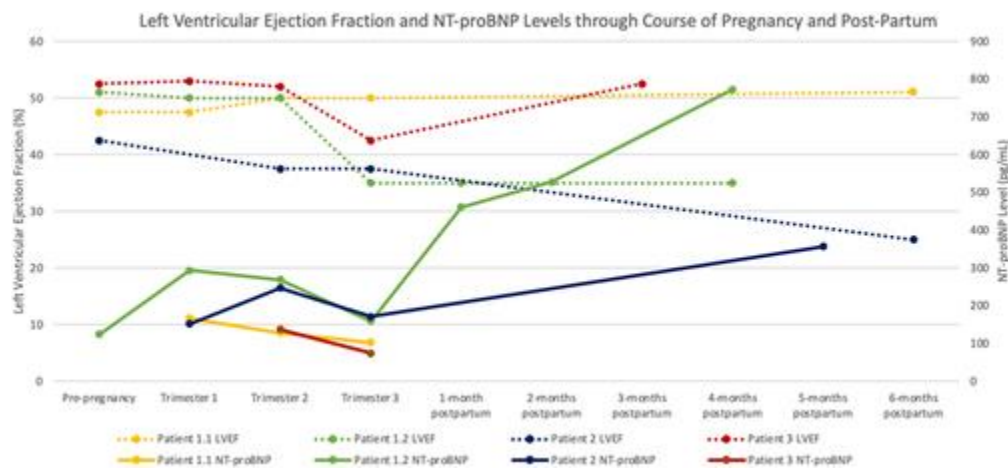
Even though men and women differ in the etiology of TR, both sexes show similar survival rates after TTVI. The TAPSE/mPAP ratio can improve prognostication after TTVI, and sex-specific thresholds should be applied to guide future patient selection.

## 6. Cardiac Complications of Pregnancy in Desmoplakin Cardiomyopathy

### Introduction

Pathogenic variants in the *DSP* gene, which encodes the desmosomal protein desmoplakin (DSP), are present in approximately 4% of adults who undergo genetic testing for dilated cardiomyopathy.<sup>1</sup> The phenotype of *DSP* cardiomyopathy is of predominant left ventricular (LV) involvement with episodic myocardial injury or inflammation, heart failure, and a heavy burden of ventricular arrhythmias.<sup>2</sup> Although the overlapping genetic etiology of peripartum and dilated cardiomyopathy was recently described, there are no descriptions of pregnancy outcomes in patients with pre-

existing *DSP* cardiomyopathy. Studies in arrhythmogenic right ventricular cardiomyopathy have described a modest burden of ventricular tachycardia or heart failure (3 and 2 episodes, respectively, in 196 pregnancies).<sup>3</sup> In this study, we identified 3 patients who had a prenatal diagnosis of *DSP* cardiomyopathy by using the STORCC (Standardized Outcomes in Reproductive Cardiovascular Care) registry from 2011 to 2022,<sup>4</sup> and we report their prospectively observed 4 pregnancies.



### Patient 1: Pregnancy 1

A 27-year-old gravida 1, para 0 woman underwent in vitro fertilization (IVF) during which preimplantation genetic testing was used to prevent transmission of the *DSP* variant. She had symptomatic premature ventricular contractions (PVCs) beginning 4 years before pregnancy that were treated with nadolol and radiofrequency ablation on 3 occasions. Prepregnancy evaluations included cardiac magnetic resonance imaging revealing an LV ejection fraction (LVEF) of 50% and nearly circumferential, epicardial late gadolinium enhancement involving the basal and middle left ventricle. Genetic testing revealed a heterozygous, likely pathogenic variant in *DSP* c.7563\_7566del (p. Asp2521Glufs\*39). A primary prevention subcutaneous (SC) implantable

cardioverter-defibrillator (ICD) was implanted 2 years before pregnancy. A preconception echocardiogram revealed normal biventricular size, an LVEF of 50%, and mildly depressed right ventricular systolic function. Nadolol was continued during pregnancy for treatment of PVCs.

Throughout pregnancy, she experienced worsening palpitations, orthopnea, and intermittent effort intolerance. However, LVEF by echocardiography remained stable, she did not develop signs of congestion, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels remained within the normal range. She underwent induction of labor at 37.9 weeks for nonreassuring fetal testing results and was monitored on telemetry intrapartum without events. Delivery was complicated by a postpartum hemorrhage (estimated blood loss >1,000 mL) and neonatal hypoglycemia. She breastfed without complications.

Some improvement in dyspnea was noted during the postpartum period; however, palpitations increased, and Holter monitoring revealed nonsustained ventricular tachycardia (NSVT) and 2.4% PVCs.

### **Patient 1: Pregnancy 2**

The following year, the same woman presented with a spontaneous pregnancy. Her first trimester echocardiogram imaging was stable. She continued on nadolol, and metoprolol tartrate was taken as needed for increasing palpitations in the first trimester.

At 35 weeks' gestation, she developed orthopnea, paroxysmal nocturnal dyspnea, and increasing palpitations. She was hospitalized at 38 weeks after an echocardiogram revealed worsening systolic function (LVEF, 35%), and venous congestion was noted on examination. NT-proBNP levels were stable from first trimester levels at 251 pg/mL. She was treated with furosemide, and labor was induced at 38 weeks, with telemetry monitoring. She had an uncomplicated vaginal delivery of a healthy infant.



The patient required furosemide in the postpartum period for recurring dyspnea but had no further congestion on examination. However, NT-proBNP levels rose, and systolic function remained impaired 2 and 4 months after delivery (**Figure 1**). The patient continued taking metoprolol and diuretic agents, including spironolactone and furosemide. She again chose to breastfeed, and angiotensin type II receptor blockers were held.

## **Patient 2**

A 32-year-old gravida 2, para 1 woman presented in her first trimester after a spontaneous conception. Arrhythmia history included a previous cardiac arrest after which an SC ICD was placed, frequent PVCs, and atrioventricular nodal re-entrant tachycardia treated by ablation. Genetic testing before pregnancy revealed a heterozygous, likely pathogenic variant in *DSP* c.1751delA (p. Glu584fs\*52). Continuing palpitations following ablation prompted implantation of a loop recorder, present during pregnancy. At baseline, the patient reported NYHA functional class II capacity. Metoprolol succinate and aspirin were continued throughout pregnancy.

An echocardiogram obtained 2.5 years before pregnancy revealed an LVEF of 40% and low-normal right ventricular (RV) systolic function. Repeat echocardiogram imaging obtained at 14 weeks' gestation revealed worsening systolic dysfunction (LVEF, 35%). Cardiopulmonary exercise testing performed at 16 weeks revealed a decline in functional capacity, with a peak oxygen consumption of 15 mg/kg/min (56% predicted), blunted systolic blood pressure response (90 and 96 mmHg at rest and peak exercise, respectively), and frequent multifocal PVCs. Given her poor functional capacity and high risk of progressive heart failure, she was advised to consider pregnancy termination; however, she elected to continue the pregnancy. She remained stable from a cardiovascular standpoint throughout the remainder of the pregnancy. Echocardiograms at 22 and 35 weeks' gestation revealed unchanged LVEFs. No additional cardiac

medications were required during pregnancy. She was observed antenatally for a short cervix.

The patient had an uncomplicated spontaneous vaginal delivery at 37.6 weeks. She was monitored with telemetry throughout labor and for 12 hours post partum without events. The infant developed tachypnea resulting in neonatal intensive care unit (NICU) admission. Genetic testing revealed that the infant was positive for the *DSP* variant. There were no maternal postpartum complications following pregnancy, and the patient breastfed without concerns. At 18 months post partum, she was without congestion or worsening symptoms, and an echocardiogram revealed an LVEF of 25%.

### **Patient 3**

A 32-year-old gravida 2, para 1 woman underwent IVF with preimplantation genetic testing, resulting in a monochorionic, diamniotic twin pregnancy. The patient experienced a cardiac arrest 10 years earlier, for which an SC ICD was placed. Preconception cardiac evaluations included stress testing and echocardiography. Genetic testing performed 1 year before pregnancy revealed a heterozygous pathogenic variant in *DSP* c.2236del (p. Val746Tyrfs\*19). Cardiac medications included nadolol, continued throughout pregnancy for symptomatic PVCs. An echocardiogram in the first trimester revealed an LVEF of 50% and normal RV size and function. NT-proBNP levels were within the normal range (137 pg/mL). ICD interrogation in the second trimester revealed rare NSVT. The patient remained clinically stable without sustained arrhythmias. In the third trimester, there was a modest decline in LVEF to 45%, although LVEF remained low normal and stable thereafter.

The pregnancy was complicated by intrauterine growth restriction (IUGR) of both twins and oligohydramnios during the third trimester. The patient was consequently admitted at 33.9 weeks' gestation for induction of labor. Vaginal delivery was planned with telemetry monitoring during active labor. However,

nonreassuring fetal heart tracings after induction prompted urgent cesarean delivery. The patient tolerated the procedure well, and telemetry was continued for 6 hours after delivery. Both neonates were admitted to the NICU for prematurity.

The patient remained stable in the postpartum period. Her echocardiogram was unchanged. Nadolol dosage had been decreased (from 80 mg to 40 mg) during the third trimester in response to the finding of IUGR but was increased back to 80 mg post partum for recurrence of palpitations. There were no new arrhythmias or other cardiac complications. The patient successfully breastfed through the postpartum period.

## **Discussion**

Among 4 pregnancies in 3 patients with *DSP* cardiomyopathy, a decline in systolic function was observed in 2 pregnancies, symptoms of congestive heart failure accompanied by systolic functional decline occurred in 1 patient, and there were no cases of malignant arrhythmias. All patients received preconception counseling with a cardiologist and a maternal-fetal specialist, and the plan for cardiac monitoring and contingencies for worsening cardiac function were discussed. All 4 deliveries were well tolerated from a cardiac perspective, including the postpartum hemorrhage in 1 patient. Of note, vaginal deliveries were completed in 3 of the 4 pregnancies, and the 1 cesarean delivery was performed for noncardiac complications of induction, thus suggesting the safety of vaginal delivery in patients with cardiomyopathies. Findings from these 4 pregnancies suggest that there may be an increased risk of decline in systolic function during pregnancy among patients with *DSP* cardiomyopathy. These observations suggest that patients will need careful echocardiographic follow-up throughout pregnancy and in the postpartum period. It is important that patients with *DSP* cardiomyopathy who wish to become pregnant undergo prepregnancy counseling and are followed closely by a multidisciplinary cardio-obstetric team. Furthermore, the unique phenotype of and potentially increased

risk for systolic decline during pregnancy in patients with *DSP* cardiomyopathy support the recommendation for genetic testing in patients with undiagnosed cardiomyopathies to tailor cardiac and obstetric care to these patients appropriately. Future studies of patients with *DSP* cardiomyopathy will be necessary to guide clinical recommendations for this group of patients.

## **7. Stress CMR in Suspected Ischemic Heart Disease in Women**

Study Questions:

What is the effect of sex on the prognostic utility and downstream invasive revascularization and costs of stress perfusion cardiac magnetic resonance (CMR) for suspected cardiovascular disease (CVD)?

Methods:

The investigators evaluated sex-specific prognostic performance in a 2,349-patient multicenter SPINS (Stress CMR Perfusion Imaging in the United States [SPINS] Study) registry. The primary outcome measure was a composite of cardiovascular death and nonfatal myocardial infarction; secondary outcomes were hospitalization for unstable angina or heart failure, and late unplanned coronary artery bypass grafting. Cumulative incidence curves were generated by plotting cumulative incidence of primary or secondary outcome by time of follow-up, stratified by sex and stress CMR results. Significance was compared by means of the log-rank test.

Results:

SPINS included 1,104 women (47% of cohort); women had higher prevalence of chest pain (62% vs. 50%;  $p < 0.0001$ ) but lower use of medical therapies. At the 5.4-year median follow-up, women with normal stress CMR had a low annualized rate of the primary composite outcome similar to men (0.54%/y vs. 0.75%/y, respectively;  $p = \text{NS}$ ). In contrast, women with abnormal CMR were at higher risk

for both primary (3.74%/y vs. 0.54%/y;  $p < 0.0001$ ) and secondary (9.8%/y vs. 1.6%/y;  $p < 0.0001$ ) outcomes compared with women with normal CMR. Abnormal stress CMR was an independent predictor for the primary (hazard ratio [HR], 2.64; 95% confidence interval [CI], 1.20-5.90;  $p = 0.02$ ) and secondary (HR, 2.09; 95% CI, 1.43-3.08;  $p < 0.0001$ ) outcome measures. There was no effect modification for sex. Women had lower rates of invasive coronary angiography (ICA; 3.6% vs. 7.3%;  $p = 0.0001$ ) and downstream costs (\$114 vs. \$171;  $p = 0.001$ ) at 90 days following CMR. There was no effect of sex on diagnostic image quality.

Conclusions:

The authors report that stress CMR demonstrated excellent prognostic performance with lower rates of ICA referral in women.

## **8. 2023 HRS Guidance on Management of Arrhythmias During Pregnancy: Key Points**

The following are key points to remember from a Heart Rhythm Society (HRS) Expert Consensus Statement on the management of arrhythmias during pregnancy:

1. Pregnant patients with cardiac arrhythmias should be cared for by a cardio-obstetrics team that includes specialists from maternal-fetal medicine, cardiology/electrophysiology, anesthesiology, and neonatology. Shared decision making about the risks and benefits of medications and procedures, as well as risks of withholding such therapies, is recommended.
2. Palpitations are common in pregnancy and are usually benign. Patients should have a detailed history, physical examination, blood pressure testing, and resting 12-lead electrocardiogram. Unless there are concerns

for electrical or structural heart disease, most patients with modest sinus tachycardia or extrasystoles do not need additional testing.

3. Patients with a family history of inherited arrhythmia syndrome or arrhythmogenic cardiomyopathy should have an evaluation, counseling, and consideration of genetic testing.
4. During pregnancy, metoprolol, propranolol, nadolol, quinidine, and sotalol are considered safe; mexiletine can be used with caution. When breastfeeding, metoprolol, propranolol, quinidine, and sotalol are considered safe; mexiletine and nadolol can be used with caution.
5. Direct current cardioversion or defibrillation is indicated for unstable supraventricular tachycardia or ventricular tachycardia with energy dosing as in the nonpregnant patient. Synchronized cardioversion is indicated if the pregnant patient is refractory to medical therapy or has contraindications. Avoid placing electrode pads on breast tissue to improve current delivery.
6. Catheter ablation procedures during pregnancy should use techniques to minimize radiation exposure to as low as reasonably achievable. Placing a pelvic lead apron over the patient does not substantially reduce fetal radiation and is not recommended.
7. For cardiac interventions performed during pregnancy, general anesthesia is preferred over regional, left lateral tilt positioning is recommended, anesthetic medications should be reviewed to avoid exacerbation of arrhythmias, and intraprocedural fetal monitoring may be needed.
8. The route of delivery (vaginal or cesarean) should be selected according to obstetric indications. Antiarrhythmic drug therapy should be continued, and pain control optimized.
9. During lactation, antiarrhythmic medication should be continued as indicated, with preference for medications with the best safety profile. Amiodarone is generally avoided during pregnancy and lactation, but certain situations may warrant discussion of risks/benefits and shared decision making.

10. Advanced cardiac life support (ACLS) is generally performed as in the nonpregnant patient, including standard ACLS medications and defibrillation energy doses. Cardiopulmonary resuscitation performed later in pregnancy (when the uterine fundus is above the maternal umbilicus) should include leftward and upward uterine displacement.

## **9. Too Little of a Good Thing: Strong Associations Between Cardiac Size and Fitness Among Women**

### **Background**

Cardiorespiratory fitness (CRF) is associated with functional impairment and cardiac events, particularly heart failure (HF). However, the factors predisposing women to low CRF and HF remain unclear.

### **Objectives**

This study sought to evaluate the association between CRF and measures of ventricular size and function and to examine the potential mechanism linking these factors.

### **Methods**

A total of 185 healthy women aged >30 years ( $51 \pm 9$  years) underwent assessment of CRF (peak volume of oxygen uptake [ $Vo_{2peak}$ ]) and biventricular volumes at rest and during exercise by using cardiac magnetic resonance (CMR). The relationships among  $Vo_{2peak}$ , cardiac volumes, and echocardiographic measures of systolic and diastolic function were assessed using linear regression. The effect of cardiac size on cardiac reserve (change in cardiac function during exercise) was assessed by comparing quartiles of resting left ventricular end-diastolic volume (LVEDV).

## **Results**

$\text{Vo}_2$ peak was strongly associated with resting measures of LVEDV and right ventricular end-diastolic volume ( $R^2 = 0.58-0.63$ ;  $P < 0.0001$ ), but weakly associated with measures of resting left ventricular (LV) systolic and diastolic function ( $R^2 = 0.01-0.06$ ;  $P < 0.05$ ). Increasing LVEDV quartiles were positively associated with cardiac reserve, with the smallest quartile showing the smallest reduction in LV end-systolic volume (quartile [Q]1: -4 mL vs Q4: -12 mL), smallest augmentation in LV stroke volume (Q1: +11 mL vs Q4: +20 mL) and cardiac output (Q1: +6.6 L/min vs Q4: +10.3 L/min) during exercise (interaction  $P < 0.001$  for all).

## **Conclusions**

A small ventricle is strongly associated with low CRF because of the combined effect of a smaller resting stroke volume and an attenuated capacity to increase with exercise. The prognostic implications of low CRF in midlife highlight the need for further longitudinal studies to determine whether women with small ventricles are predisposed to functional impairment, exertional intolerance, and HF later in life.

## **10. Sex-Specific Stress Perfusion Cardiac Magnetic Resonance Imaging in Suspected Ischemic Heart Disease: Insights From SPINS Retrospective Registry**

### **Background**

Cardiovascular disease (CVD) remains the leading cause of mortality in women, but current noninvasive cardiac imaging techniques have sex-specific limitations.



## **Objectives**

In this study, the authors sought to investigate the effect of sex on the prognostic utility and downstream invasive revascularization and costs of stress perfusion cardiac magnetic resonance (CMR) for suspected CVD.

## **Methods**

Sex-specific prognostic performance was evaluated in a 2,349-patient multicenter SPINS (Stress CMR Perfusion Imaging in the United States [SPINS] Study) Registry. The primary outcome measure was a composite of cardiovascular death and nonfatal myocardial infarction; secondary outcomes were hospitalization for unstable angina or heart failure, and late unplanned coronary artery bypass grafting.

## **Results**

SPINS included 1,104 women (47% of cohort); women had higher prevalence of chest pain (62% vs 50%;  $P < 0.0001$ ) but lower use of medical therapies. At the 5.4-year median follow-up, women with normal stress CMR had a low annualized rate of primary composite outcome similar to men (0.54%/y vs 0.75%/y, respectively;  $P = \text{NS}$ ). In contrast, women with abnormal CMR were at higher risk for both primary (3.74%/y vs 0.54%/y;  $P < 0.0001$ ) and secondary (9.8%/y vs 1.6%/y;  $P < 0.0001$ ) outcomes compared with women with normal CMR. Abnormal stress CMR was an independent predictor for the primary (HR: 2.64 [95% CI: 1.20-5.90];  $P = 0.02$ ) and secondary (HR: 2.09 [95% CI: 1.43-3.08];  $P < 0.0001$ ) outcome measures. There was no effect modification for sex. Women had lower rates of invasive coronary angiography (3.6% vs 7.3%;  $P = 0.0001$ ) and downstream costs (\$114 vs \$171;  $P = 0.001$ ) at 90 days following CMR. There was no effect of sex on diagnostic image quality.

## **Conclusions**

Stress CMR demonstrated excellent prognostic performance with lower rates of invasive coronary angiography referral in women. Stress CMR should be considered as a first-line noninvasive imaging tool for the evaluation of women. (Stress CMR Perfusion Imaging in the United States [SPINS] Study)

## **11. LDL lowering effect of PCSK9 inhibition is reduced in women**

### **Aims**

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a key regulator of plasma low-density lipoprotein cholesterol (LDL-C) concentration, and its inhibition reduces the risk of atherosclerotic cardiovascular disease (ASCVD). We aimed to assess the sex-differential effect of either pharmacological or genetic inhibition of PCSK9 on LDL-C levels.

### **Methods and results**

We meta-analyzed six real-life studies (1216 men and 641 women) that investigated the effects of PCSK9 monoclonal antibodies (mAbs) on LDL-C reduction in men and women. Despite higher LDL-C levels in women at baseline [mean difference (MD) = 17.4 mg/dL,  $P < 0.0001$ , women = 175 mg/dL vs. men = 152 mg/dL], the LDL-C reduction under PCSK9 mAb treatment was significantly greater in men (MD = 7.6 mg/dL, 95% confidence interval: 2.7–12.4,  $P = 0.002$ ) than in women.

We tested the sex-related association of the *loss-of-function* variant *PCSK9-R46L* with LDL-C plasma levels in 382 813 individuals (219 301 women and 163 512 men) free of lipid-lowering drugs from the UK Biobank general population cohort. The magnitude of LDL-C reduction was larger in men than in women (mean LDL-C difference: –35 mg/dL vs. –26 mg/dL, when comparing homozygous carriers with non-carriers in men and women, respectively). The relationship

between *PCSK9*-R46L and LDL-C was significantly dependent on sex ( $P$  for interaction =  $7.2e-04$ ).

### **Conclusion**

These results demonstrate by complementary approaches that the decrease in LDL-C mediated by *PCSK9* inhibition is slightly, but significantly, less marked in women than in men. These data reinforce the need for specific studies to develop sex-specific recommendations for the management of ASCVD in women.

## **12. COVID-19 Booster Vaccination in Early Pregnancy and Surveillance for Spontaneous Abortion**

### OBJECTIVE

To evaluate whether there is an association between COVID-19 booster vaccination during pregnancy and spontaneous abortion.

### DESIGN, SETTING, AND PARTICIPANTS

This observational, case-control, surveillance study evaluated people aged 16 to 49 years with pregnancies at 6 to 19 weeks' gestation at 8 health systems in the Vaccine Safety Datalink from November 1, 2021, to June 12, 2022. Spontaneous abortion cases and ongoing pregnancy controls were evaluated during consecutive surveillance periods, defined by calendar time.

### EXPOSURE

Primary exposure was receipt of a third messenger RNA (mRNA) COVID-19 vaccine dose within 28 days before spontaneous abortion or index date (midpoint of surveillance period in ongoing pregnancy controls). Secondary exposures were third mRNA vaccine doses in a 42-day window or any COVID-19 booster in 28- and 42-day windows.

### MAIN OUTCOMES AND MEASURES

Spontaneous abortion cases and ongoing pregnancy controls were identified from electronic health data using a validated algorithm. Cases were assigned to

a single surveillance period based on pregnancy outcome date. Eligible ongoing pregnancy time was assigned to 1 or more surveillance periods as an ongoing pregnancy-period control. Generalized estimating equations were used to estimate adjusted odds ratios (AOR) with gestational age, maternal age, antenatal visits, race and ethnicity, site, and surveillance period as covariates and robust variance estimates to account for inclusion of multiple pregnancy periods per unique pregnancy.

## RESULTS

Among 112 718 unique pregnancies included in the study, the mean (SD) maternal age was 30.6 (5.5) years. Pregnant individuals were Asian, non-Hispanic (15.1%); Black, non-Hispanic (7.5%); Hispanic (35.6%); White, non-Hispanic (31.2%); and of other or unknown (10.6%); and 100% were female. Across eight 28-day surveillance periods, among 270 853 ongoing pregnancy-period controls, 11 095 (4.1%) had received a third mRNA COVID-19 vaccine in a 28-day window; among 14 226 cases, 553 (3.9%) had received a third mRNA COVID-19 vaccine within 28 days of the spontaneous abortion. Receipt of a third mRNA COVID-19 vaccine was not associated with spontaneous abortion in a 28-day window (AOR, 0.94; 95% CI, 0.86-1.03). Results were consistent when using a 42-day window (AOR, 0.97; 95% CI, 0.90-1.05) and for any COVID-19 booster in a 28-day (AOR, 0.94; 95% CI, 0.86-1.02) or 42-day (AOR, 0.96; 95% CI, 0.89-1.04) exposure window.

## CONCLUSIONS AND RELEVANCE

In this case-control surveillance study, COVID-19 booster vaccination in pregnancy was not associated with spontaneous abortion. These findings support the safety of recommendations for COVID-19 booster vaccination, including in pregnant populations.

### **13. Sex Difference in the Outcomes of Acute Myocardial Infarction in Young Patients**

#### BACKGROUND

Younger women experience worse health status than men after their index episode of acute myocardial infarction (AMI). However, whether women have a higher risk for cardiovascular and noncardiovascular hospitalizations in the year after discharge is unknown.

#### OBJECTIVES

The aim of this study was to determine sex differences in causes and timing of 1-year outcomes after AMI in people aged 18 to 55 years.

#### METHODS

Data from the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) study, which enrolled young patients with AMI across 103 U.S. hospitals, were used. Sex differences in all-cause and cause-specific hospitalizations were compared by calculating incidence rates ([IRs] per 1,000 person-years) and IR ratios with 95% CIs. We then performed sequential modeling to evaluate the sex difference by calculating subdistribution HRs (SHRs) accounting for deaths.

#### RESULTS

Among 2,979 patients, at least 1 hospitalization occurred among 905 patients (30.4%) in the year after discharge. The leading causes of hospitalization were coronary related (IR: 171.8 [95% CI: 153.6-192.2] among women vs 117.8 [95% CI: 97.3-142.6] among men), followed by noncardiac hospitalization (IR: 145.8 [95% CI: 129.2-164.5] among women vs 69.6 [95% CI: 54.5-88.9] among men). Furthermore, a sex difference was present for coronary-related hospitalizations (SHR: 1.33; 95% CI: 1.04-1.70; P = 0.02) and noncardiac hospitalizations (SHR: 1.51; 95% CI: 1.13-2.07; P = 0.01).

## CONCLUSIONS

Young women with AMI experience more adverse outcomes than men in the year after discharge. Coronary-related hospitalizations were most common, but noncardiac hospitalizations showed the most significant sex disparity.

### **14. Risk of Hypertension Up With Use of Oral Estrogen-Only Hormone Therapy**

For postmenopausal women using estrogen-only hormone therapy (HT), oral estrogen-only HT use is associated with increased risk of hypertension, according to a study published online June 5 in *Hypertension*.

Cindy Z. Kalenga, from the Cumming School of Medicine at the University of Calgary in Canada, and colleagues conducted a population-based cohort study involving women aged  $\geq 45$  years who filled at least two consecutive prescriptions for estrogen-only HT to examine the association between route of administration with hypertension risk. Data were included for 112,240 women who used an estrogen-only form of HT.

The researchers found that compared with transdermal and vaginal estrogens, oral estrogen was associated with a higher risk of hypertension (hazard ratios, 1.14 and 1.19, respectively). Compared with estradiol, conjugated equine estrogen was associated with increased risk of hypertension (hazard ratio, 1.08); no increased risk was seen for estrone. Positive associations were seen for duration of estrogen exposure and cumulative dose of estrogen with risk of hypertension.

"It's really important to have greater knowledge on safe and effective hormonal treatments for women during menopause," a coauthor said in a statement. "At the end of the day, it's an individualized decision about what is best for the person going through menopause and should include open dialogue with their physician or health care team."

## **15. Sex-specific aortic valve calcifications in patients undergoing transcatheter aortic valve implantation**

### **Aims**

To study sex-specific differences in the amount and distribution of aortic valve calcification (AVC) and to correlate the AVC load with paravalvular leakage (PVL) post-transcatheter aortic valve intervention (TAVI).

### **Methods and results**

This registry included 1801 patients undergoing TAVI with a Sapien3 or Evolut valve in two tertiary care institutions. Exclusion criteria encompassed prior aortic valve replacement, suboptimal multidetector computed tomography (MDCT) quality, and suboptimal transthoracic echocardiography images. Calcium content and distribution were derived from MDCT. In this study, the median age was 81.7 (25th–75th percentile 77.5–85.3) and 54% male. Men, compared to women, were significantly younger [81.2 (25th–75th percentile 76.5–84.5) vs. 82.4 (78.2–85.9),  $P \leq 0.01$ ] and had a larger annulus area [512 mm<sup>2</sup> (25th–75th percentile 463–570) vs. 405 mm<sup>2</sup> (365–454),  $P < 0.01$ ] and higher Agatston score [2567 (25th–75th percentile 1657–3913) vs. 1615 (25th–75th percentile 905–2484),  $P < 0.01$ ]. In total, 1104 patients (61%) had none-trace PVL, 648 (36%) mild PVL, and 49 (3%) moderate PVL post-TAVI. There was no difference in the occurrence of moderate PVL between men and women (3% vs. 3%,  $P = 0.63$ ). Cut-off values for the Agatston score as predictor for moderate PVL based on the receiver-operating characteristic curve were 4070 (sensitivity 0.73, specificity 0.79) for men and 2341 (sensitivity 0.74, specificity 0.73) for women.

### **Conclusion**

AVC is a strong predictor for moderate PVL post-TAVI. Although the AVC load in men is higher compared to women, there is no difference in the incidence of moderate PVL. Sex-specific Agatston score cut-offs to predict moderate PVL were almost double as high in men vs. women.

## **16. Journal Series Explores How Eroding Abortion Access Impacts the HF Community**

The *Journal of Cardiac Failure* is launching a series that will explore the intersection of reproductive health and heart failure (HF) care following the loss of federal abortion protections in the United States nearly a year ago.

The series debuted this week with a perspective delving into pregnancy in the context of left ventricular assist device (LVAD) implantation.

Once it became clear that the US Supreme Court would be using the *Dobbs v. Jackson Women's Health Organization* case to overturn the 50-year-old *Roe v. Wade* decision, cardiologists—particularly from the HF community—predicted a detrimental impact on the care of their high-risk patients, many of whom would be placing their lives at risk were they to become pregnant.. Over the ensuing months, concerns have mounted as state-level abortion restrictions continue to spread.

During that time, editors of the *Journal of Cardiac Failure (JCF)* received a submitted perspective on pregnancy among patients with LVADs, which sparked the idea for a larger series of pieces focused on the care of patients with HF in the post-Roe era, according to Nosheen Reza, MD (University of Pennsylvania, PA), an associate editor of the journal. Now published, the LVAD perspective, with lead author Karen Flores Rosario, MD (Duke University Hospital, Durham, NC), is the first in the series, with several other articles planned for the coming months.

The recurring feature was announced in a *JCF* "Editor's Page" article by Reza, Editor-in-Chief Robert Mentz, MD (Duke University Medical Center, Durham, NC), and Deputy Editor Anu Lala, MD (Icahn School of Medicine at Mount Sinai, New York, NY).



“In the process of reviewing the [LVAD] piece, we thought wouldn’t it be great to really expand this conversation and make *JCF* a home . . . and a platform to facilitate the ongoing dialog and education relevant to the care of our patients across the spectrum of heart failure,” Reza told TCTMD.

Forthcoming perspectives will tackle pregnancy among patients with HF in general, as well as those undergoing heart transplantation, with adult congenital heart disease, and with pulmonary hypertension. There also will be a piece presenting a personal perspective from a trainee, Reza noted, adding that it’s possible the series will expand from there. “I imagine that we would be open to obviously facilitating ongoing dialog in this space, and we’re really interested in what our readership has to say.”

Reza underscored the seriousness of the discussion by noting that cardiovascular disease is a leading cause of maternal mortality, which is already more of a problem in the US than in other developed nations and continues to worsen. The new *JCF* series is meant to highlight that women with heart failure are at a particularly high risk compared with others, she said.

“We thought it was important to really educate our community on these issues, really provide these kinds of data about why these populations may be at elevated risk if therapeutic options like elective termination are no longer available and how we can modify our practices to mitigate these risks, not only when a pregnant person with heart failure arrives to our clinic but obviously in the processes before that,” Reza said.

In terms of how practice can be changed now, Reza suggested implementation of preconception counseling for all female patients with advanced cardiovascular disease, the generation of evidence to inform specific guidelines around those discussions, and use of innovative care models that facilitate access to family planning clinics as part of an LVAD evaluation, for instance.

“I’m excited to have those themes echoed throughout these pieces, and I think it’s part of our goal to really inspire this conversation about how we can really change for the better the care of all of our patients,” Reza said.

### **LVADs and Pregnancy**

In their perspective, Flores Rosario et al note that about 7% of women with LVADs are of reproductive age, with most implantations used as a bridge to transplantation. Pregnancy is “often considered to be incompatible with durable LVAD therapy, although limited experience has precluded precise quantification of risks,” they add.

They discuss the need, in the current landscape, for reproductive life planning before LVAD implantation and explore how clinical management of these patients may change, including use of interdisciplinary pregnancy-care teams, incorporation of family-planning discussions and preconception counseling, and timely referral to abortion centers for patients with either unwanted or extreme-risk pregnancies.

The perspective authors also make recommendations for how LVAD programs can respond to the new situation and argue for having a framework to guide discussions touching on the intersection of pregnancy and LVADs.

### **17. US Athlete’s Death Highlights Risk of Hypertensive Disorders of Pregnancy**

Tori Bowie, a highly decorated American track and field star, died from pregnancy-related complications that may have included eclampsia, according to an autopsy report released this week from the Orange Country, FL, medical examiner’s office.

The 32-year-old Bowie, who won gold, silver, and bronze medals at the 2016 Olympic Games, was 8 months pregnant at the time of her death on May 2, 2023. Her death shocked the sports world, but cardiologists say her tragic case highlights the risk of hypertensive disorders in pregnancy.

Michael Honigberg, MD (Massachusetts General Hospital, Boston), a physician at the Corrigan Women's Heart Health Program, said that while many risk factors for preeclampsia are well documented, such as obesity, they don't fully capture everybody who may be at risk for developing the hypertensive disorder. Moreover, the risk of preeclampsia doesn't affect everybody equally, with African-American women, like Bowie, at a higher risk of pregnancy-related complications than white women.

"There are misconceptions about the sort of person in whom preeclampsia occurs," he told TCTMD. "It's one of the things that can be scary and challenging about it."

Her record-breaking times on the track are part of what made Bowie's death so startling. Born in Sand Hill, MS, Bowie was once the fastest woman in the world, a title she claimed after winning the 100m in 10.85 seconds at the 2017 world championships in London, England. She was also a highly decorated Olympic athlete, winning a silver medal in the 100m and a bronze medal in the 200m at the 2016 games in Rio de Janeiro, Brazil. At those Olympics, she also ran the anchor leg on the gold medal-winning 4 x 100m relay team.

"Very similar to cardiovascular disease, hypertensive disorders of pregnancy and preeclampsia tend to be more common in individuals who already have high blood pressure and in individuals who are obese or who have a higher body mass index than what we think is optimal," Natalie Bello, MD (Cedars-Sinai Medical Center, Los Angeles, CA), chair of the American College of Cardiology's Reproductive Health & Cardio-Obstetrics Council, told TCTMD. "We know that we have an obesity crisis in the country right now and around the world so a lot

of this we think is probably attributable to people having suboptimal cardiometabolic health.”

**Unfortunately, preeclampsia and hypertensive disorders of pregnancy are on the rise in the United States.**Natalie Bello

Honigberg, whose research involves the study of novel maternal genetic variants linked with preeclampsia, pointed out that while obstetrician-gynecologists screen for overt risk factors, these risk factors can miss a substantial proportion of women who could develop the disorder. There is a strong genetic component to preeclampsia, he said, which can put someone with even ideal cardiometabolic health at risk.

“We think that probably about a third of it reflects maternal genetic predisposition and another 20% reflects fetal genes,” he said. “A lot of the causal biomarkers that drive at least the late stages of this condition come from the placenta, which is a different set of genes from mom. It’s partly mom’s genes and partly dad’s genes. So it’s really complex biology and genetics.”

In a *JAMA Cardiology* study last week, Finnish researchers identified genes related to blood pressure that were associated with preeclampsia in a genome-wide association study, but showed that many of the cardiovascular disease-related genes influenced other processes as well, including cardiometabolic, endothelial, and placental function.

### **Eclampsia “Exceedingly Rare”**

Hypertensive disorders in pregnancy include chronic hypertension, gestational hypertension (high blood pressure that develops during pregnancy, particularly the latter half), and preeclampsia or eclampsia. Data from the US Centers for Disease Control and Prevention (CDC) showed that hypertensive disorders affect

roughly 1 in 7 women delivering in the hospital, with large disparities seen across racial and ethnic lines.

Preeclampsia is a condition in which a woman with normal blood pressure develops hypertension ( $\geq 140$  mm Hg systolic or  $\geq 90$  mm Hg diastolic), along with protein in the urine and other symptoms, including neurologic changes, such as headaches and visual disturbances, in the second half of pregnancy or soon after giving birth. Untreated, it can progress rapidly to eclampsia, which can lead to seizures, stroke, and death.

The progression to eclampsia is preventable if detected early, said Bello, noting the main approaches are antihypertensive medications to get blood pressure under control and the use intravenous magnesium sulfate to prevent seizures.

**There are misconceptions about the sort of person in whom preeclampsia occurs.** Michael Honigberg

In one recent study that used National Inpatient Sample (NIS) data from the Agency for Healthcare Research and Quality (AHRQ), the incidence of preeclampsia was 5.2%. In other studies, the incidence ranges from 3% to 6% of all pregnancies, depending on the region. Preeclampsia, along with other hypertensive disorders of pregnancy, increase a woman's long-term risk of cardiovascular disease.

Many physicians, including cardiologists, may not have kept pace with this research since their medical school training and may be unaware that the landscape has shifted.

“Unfortunately, preeclampsia and hypertensive disorders of pregnancy are on the rise in the United States,” said Bello. “Eclampsia, thankfully, is quite rare.

That's why with having an awareness of the signs of symptoms that are indicative of preeclampsia or impending preeclampsia, and getting medical attention quickly, our hope is that we can treat people with magnesium, lower their blood pressure, and prevent that progression."

Other risk factors for preeclampsia include a history of autoimmune disorders, advanced maternal age, a history of chronic kidney disease, and first pregnancy (not including miscarriages or abortions). Multiple studies have shown that Black women have the highest risk of the disorder compared with other racial/ethnic groups, with estimates showing the prevalence of preeclampsia is approximately 60% higher compared with white women.

To TCTMD, Honigberg said it's not entirely clear why Black women are more likely to develop preeclampsia, although there is a strong suspicion that the various social determinants of health drive the racial disparity.

"Exactly how that translates to the extremely complex biology of this condition, we still don't really understand all of those steps," he said. "We know that Black women in the US are more likely to have overt cardiometabolic risk factors strongly linked to preeclampsia. Things like pre-pregnancy chronic hypertension, pre-pregnancy prediabetes or diabetes, pre-pregnancy overweight or obesity—that's part of it, but I don't think it explains all of it. We don't have the sort of high-quality, robust data that clearly explains the reason [for higher rates among Black women]."

In 2021, the CDC reported that 1,205 women died while pregnant, or within 42 days of terminating the pregnancy, which was up from 861 deaths in 2020 and 754 deaths in 2019. The maternal mortality rate for Black women was 2.5 times higher than that for white women in 2021.

### **Maternal Mortality Higher in Black Americans**

Bello said the unfortunate death of Tori Bowie emphasizes the importance of patient/physician discussions about pregnancy, particularly if they may be at risk for preeclampsia or other hypertensive disorders. “I like to educate my patients about what are the warning signs of preeclampsia and eclampsia,” she said. “It’s a little tricky because there can be some overlap with the physiologic changes of pregnancy and the signs of preeclampsia.”

Swelling, particularly over a short period of time, nausea, headaches, or visual changes should all be considered as potential signs of preeclampsia, said Bello. “I would say always in pregnancy, err on the side of caution and check with your doctor,” she said. High blood pressure, she added, is a silent killer, so it’s important for women to have their blood pressure checked at every prenatal visit, which is a US Preventive Services Task Force recommendation. For women at high risk for preeclampsia, the American College of Obstetricians and Gynecologists (ACOG) recommends low-dose aspirin started after 12 weeks gestation and continued until pregnancy.

In 2022, the Chronic Hypertension and Pregnancy (CHAP) trial, which was funded by the National Heart, Lung, and Blood Institute, showed that treating pregnant women with mild, chronic hypertension to a target of less than 140/90 mm Hg was associated with significantly better pregnancy outcomes and no signal of harm to the mother or baby.

Honigberg said there is more-uniform practice around controlling blood pressure since the CHAP trial was published, noting there had been some initial concerns about the effects of lower blood pressure on fetal growth. Many of the other recommendations to prevent or treat preeclampsia include typical heart-healthy recommendations, such as eating a healthy diet (preferably a Mediterranean one) and exercising, as well as maintaining a body mass index as normal as possible.

## **18. ACC CardiaCast: Women are Not Little Men: Reproductive Risk Factors and Long-Term CVD Risk**

“Women are Not Little Men” is a new podcast series within CardiaCast designed for cardiovascular health providers to increase awareness of sex-based differences in cardiovascular disease (CVD) and to improve the clinical care of women with CVD. “Women are Not Little Men” is hosted by Drs. Emily Lau and Niti Aggarwal, nationally renowned experts in women’s CVD and members of the American College of Cardiology CVD in Women Committee. In this episode, Drs. Kathryn Lindley and Erin Michos discuss unique female-specific CVD risk factors across a woman’s lifespan, including adverse pregnancy outcomes and menopause.

## **19. Change in Birthweight Across Pregnancies Tied to Cardiovascular Mortality**

Changes in offspring birthweight quartiles from first to second pregnancy could inform women's future risk of cardiovascular disease (CVD) death, according to a study published online May 30 in the *American Journal of Epidemiology*.

Yeneabebe Tilahun Sima, Ph.D., from the University of Bergen in Norway, and colleagues assessed long-term CVD mortality by offspring birth weight patterns among women with spontaneous and iatrogenic term deliveries in Norway (1967 to 2020).

The researchers found that changes in offspring birth weight quartiles were associated with long-term maternal CVD mortality. Women with a first offspring in quartile 2/3 (Q2/Q3) and a second in quartile 1 had higher mortality risk (hazard ratio [HR], 1.33; 95 percent confidence interval [CI], 1.18 to 1.50), compared with women who had two term infants in Q2/Q3. Risk of CVD mortality was lower if the second offspring was in quartile 4 (HR, 0.78; 95 percent CI, 0.67 to 0.91). Having a second offspring in quartile 4 offset the risk associated with having a first infant in quartile 1 (HR, 0.99; 95 percent CI, 0.75 to 1.31). These patterns were similar regardless of iatrogenic or spontaneous deliveries.



"Our findings highlight the importance of including information from women's subsequent births for identification of high-risk subgroups for specific follow-up,"

## **20. Exercise positively impacts global longitudinal strain (GLS) in women at risk of developing cardiovascular disease**

### **Background/Introduction**

Cardiovascular (CV) disease accounts for one in three deaths in women globally each year, with hypertension (HTN) and type 2 diabetes (T2DM) recognised as primary modifiable risk factors for its development. Global longitudinal strain (GLS) is a highly sensitive CV imaging measure that detects early signs of myocardial dysfunction prior to clinical abnormalities arising, and is a strong prognostic indicator for future CV dysfunction and mortality. However, the effect of exercise on GLS in women with HTN or T2DM is unclear.

### **Purpose**

This study aimed to determine if exercise positively impacts GLS in women with HTN or T2DM. Changes in peak aerobic fitness ( $VO_{2peak}$ ) were also explored.

### **Methods**

A randomised crossover trial was performed at our university between August 2021-December 2022. Fifteen women (aged  $64.1 \pm 4.7$ ) diagnosed with HTN ( $n=12$ ) and T2DM ( $n=3$ ) participated. Participants completed an 8-week exercise and 8-week control period, separated by a washout period of  $21.6 \pm 14.2$  weeks. Comprehensive 2D and 3D resting echocardiography and exercising testing were performed pre-and-post each arm to measure GLS (%) and  $VO_{2peak}$  (ml/kg/min). The exercise intervention consisted of three supervised aerobic exercise sessions per week for eight consecutive weeks, performed at a moderate intensity. Nine participants were required to provide 80% power to detect an absolute mean difference in GLS of 1.7 between groups (10% relative change in GLS from a baseline GLS of -17%), with an alpha of 0.05. A linear mixed effect

model was used to compare outcomes between (exercise vs control) and within (pre- vs. post-intervention) groups for GLS and VO<sub>2</sub>peak. All participants who completed at least one arm of the trial were included in analyses.

## **Results**

Nine participants completed the crossover, with four completing the control arm only, and two completing the exercise arm only. Exercise adherence was high (86.6%). GLS (%) increased significantly following exercise ( $-16.8 \pm 1.5$  to  $-18.4 \pm 1.8$ ;  $p = <0.001$ ), but not control ( $-17.2 \pm 2.0$  to  $-16.9 \pm 1.4$ ;  $p = 0.585$ ). Similarly, a significant improvement in VO<sub>2</sub>peak (ml/kg/min) was observed following exercise ( $18.0 \pm 2.1$  to  $19.2 \pm 2.6$ ;  $p = <0.001$ ), but not control ( $17.5 \pm 2.7$  to  $17.2 \pm 2.7$ ;  $p = 0.269$ ). There was a significant between-group difference for both GLS ( $p = <0.001$ ) and VO<sub>2</sub>peak ( $p = 0.011$ ) (figure 1).

## **Conclusion(s)**

Aerobic exercise positively impacts GLS in women at risk of developing CV disease. Due to its high sensitivity, GLS could be used to measure the effectiveness of aerobic exercise programs in populations at risk of developing CV disease, before changes in traditional clinical measures are expected to occur.

## **21. Management of Arrhythmias During Pregnancy**

This international multidisciplinary expert consensus statement is intended to provide comprehensive guidance that can be referenced at the point of care to cardiac electrophysiologists, cardiologists, and other health care professionals, on the management of cardiac arrhythmias in pregnant patients and in fetuses. This document covers general concepts related to arrhythmias, including both brady- and tachyarrhythmias, in both the patient and the fetus during pregnancy. Recommendations are provided for optimal approaches to diagnosis and evaluation of arrhythmias; selection of invasive and noninvasive options for treatment of arrhythmias; and disease- and patient-specific considerations when risk stratifying, diagnosing, and treating arrhythmias in pregnant patients and

fetuses. Gaps in knowledge and new directions for future research are also identified.

## **22. Pregnancy-Induced Hypertensive Disorder and Risks of Future Ischemic and Nonischemic Heart Failure**

### BACKGROUND

Although adverse pregnancy outcomes are associated with an increased risk of cardiovascular disease, studies on timing and subtypes of heart failure after a hypertensive pregnancy are lacking.

### OBJECTIVES

The goal of this study was to assess the association between pregnancy-induced hypertensive disorder and risk of heart failure, according to ischemic and nonischemic subtypes, and the impact of disease characteristics and the timing of heart failure risks.

### METHODS

This was a population-based matched cohort study, comprising all primiparous women without a history of cardiovascular disease included in the Swedish Medical Birth Register between 1988 and 2019. Women with pregnancy-induced hypertensive disorder were matched with women with normotensive pregnancies. Through linkage with health care registers, all women were followed up for incident heart failure, classified as ischemic or nonischemic.

### RESULTS

In total, 79,334 women with pregnancy-induced hypertensive disorder were matched with 396,531 women with normotensive pregnancies. During a median follow-up of 13 years, rates of all heart failure subtypes were more common among women with pregnancy-induced hypertensive disorder. Compared with women with normotensive pregnancies, adjusted HRs (aHRs) with 95% CIs were as follows: heart failure overall, aHR: 1.70 (95% CI: 1.51-1.91); ischemic heart

failure, aHR: 2.28 (95% CI: 1.74-2.98); and nonischemic heart failure, aHR: 1.60 (95% CI: 1.40-1.83). Disease characteristics indicating severe hypertensive disorder were associated with higher heart failure rates, and rates were highest within the first years after the hypertensive pregnancy but remained significantly increased thereafter.

## CONCLUSIONS

Pregnancy-induced hypertensive disorder is associated with an increased short-term and long-term risk of incident ischemic and nonischemic heart failure. Disease characteristics indicating more severe forms of pregnancy-induced hypertensive disorder amplify the heart failure risks.

### **23. Early Hysterectomy Increases Risk for Cardiovascular Disease**

Early menopause due to hysterectomy is associated with increased risks for a composite of cardiovascular disease (CVD), according to a study published online June 12 in *JAMA Network Open*.

Jin-Sung Yuk, M.D., Ph.D., from the Inje University College of Medicine in Seoul, South Korea, and colleagues evaluated the association of hysterectomy with the risk for incident CVD among women (aged 40 to 49 years). The analysis included 55,539 pairs with and without hysterectomy matched for age, socioeconomic status, region, Charlson Comorbidity Index, hypertension, diabetes, dyslipidemia, menopause, menopausal hormone therapy, and adnexal surgery.

The researchers found that during a median 7.9 years of follow-up, the incidence of CVD was 115 per 100,000 person-years for the hysterectomy group versus 96 per 100,000 person-years for the no-hysterectomy group. The hysterectomy group had an increased risk for CVD compared with the no-hysterectomy group in an adjusted analysis (hazard ratio, 1.25). While the groups were similar for the incidence of myocardial infarction and coronary artery revascularization, the

risk for stroke was significantly higher in the hysterectomy group (hazard ratio, 1.31). Findings persisted even when excluding women who underwent oophorectomy.

"Although we found that widely performed hysterectomy with a broad indication for benign diseases at premenopausal ages slightly increases the risk of CVD, the incidence is not high, so a change in clinical practice may not be needed,"

## **24. Reductions in the Number of Stillbirths and Preterm Births Among COVID-19–Vaccinated women**

### BACKGROUND

COVID-19 infection in pregnancy is associated with a higher risk of progression to severe disease, but vaccine uptake by pregnant women is hindered by persistent safety concerns. COVID-19 vaccination in pregnancy has been shown to reduce stillbirth, but its relationship with preterm birth is uncertain.

### OBJECTIVE

This study aimed to measure the rate of COVID-19 vaccine uptake among women giving birth in Melbourne, Australia, and to compare perinatal outcomes by vaccination status.

### STUDY DESIGN

This was a retrospective multicenter cohort study conducted after the June 2021 government recommendations for messenger RNA COVID-19 vaccination during pregnancy. Routinely collected data from all 12 public maternity hospitals in Melbourne were extracted on births at  $\geq 20$  weeks' gestation from July 1, 2021 to March 31, 2022. Maternal sociodemographic characteristics were analyzed from the total birth cohort. Perinatal outcomes were compared between vaccinated and unvaccinated women for whom weeks 20 to 43 of gestation fell entirely within the 9-month data collection period. The primary outcomes were the rates of stillbirth and preterm birth (spontaneous and iatrogenic) in singleton

pregnancies of at least 24 weeks' gestation, after exclusion of congenital anomalies. Secondary perinatal outcomes included the rate of congenital anomalies among infants born at  $\geq 20$  weeks' gestation and birthweight  $\leq$  third centile and newborn intensive care unit admissions among infants born without congenital anomalies at  $\geq 24$  weeks' gestation. We calculated the adjusted odds ratio of perinatal outcomes among vaccinated vs unvaccinated women using inverse propensity score-weighting regression adjustment with multiple covariates;  $P < .05$  was considered statistically significant.

## RESULTS

Births from 32,536 women were analyzed: 17,365 (53.4%) were vaccinated and 15,171 (47.6%) were unvaccinated. Vaccinated women were more likely to be older, nulliparous, nonsmoking, not requiring an interpreter, of higher socioeconomic status, and vaccinated against pertussis and influenza. Vaccination status also varied by region of birth. Vaccinated women had a significantly lower rate of stillbirth compared with unvaccinated women (0.2% vs 0.8%; adjusted odds ratio, 0.18; 95% confidence interval, 0.09-0.37;  $P < .001$ ). Vaccination was associated with a significant reduction in total preterm births at  $< 37$  weeks (5.1% vs 9.2%; adjusted odds ratio, 0.60; 95% confidence interval, 0.51-0.71;  $P < .001$ ), spontaneous preterm birth (2.4% vs 4.0%; adjusted odds ratio, 0.73; 95% confidence interval, 0.56-0.96;  $P = .02$ ), and iatrogenic preterm birth (2.7% vs 5.2%; adjusted odds ratio, 0.52; 95% confidence interval, 0.41-0.65;  $P < .001$ ). Infants born to vaccinated mothers also had lower rates of admission to the neonatal intensive care unit. There was no significant increase in the rate of congenital anomalies or birthweight  $\leq 3$ rd centile in vaccinated women. Vaccinated women were significantly less likely to have an infant with a major congenital anomaly compared with the unvaccinated group (2.4% vs 3.0%; adjusted odds ratio, 0.72; 95% confidence interval, 0.56-0.94;  $P = .02$ ). This finding remained significant even when the analysis was restricted to women vaccinated before 20 weeks' gestation.

## CONCLUSION

COVID-19 vaccination during pregnancy was associated with a reduction in stillbirth and preterm birth, and not associated with any adverse impact on fetal growth or development. Vaccine coverage was substantially influenced by known social determinants of health.

## **25. Influence of cusp morphology and sex on quantitative valve composition in severe aortic stenosis**

### **Aims**

Aortic stenosis is characterized by fibrosis and calcification of the valve, with a higher proportion of fibrosis observed in women. Stenotic bicuspid aortic valves progress more rapidly than tricuspid valves which may also influence the relative composition of the valve.

We aimed to investigate the influence of cusp morphology on quantitative aortic valve composition quantified from contrast-enhanced computed tomography angiography in severe aortic stenosis.

### **Methods and results**

Patients undergoing transcatheter aortic valve implantation with bicuspid and tricuspid valves were propensity matched 1:1 by age, sex, and comorbidities. Computed tomography angiograms were analyzed using semi-automated software to quantify fibrotic and calcific scores (volume/valve annular area) and the fibro-calcific ratio (fibrotic score/calcific score).

The study population (n = 140) was elderly ( $76 \pm 10$  years, 62% male) and had a peak aortic jet velocity of  $4.1 \pm 0.7$  m/s. Compared to those with tricuspid valves (n = 70), patients with bicuspid valves (n = 70) had higher fibrotic scores (204 [interquartile range 118-267] versus 144[99-208] mm<sup>3</sup>/cm<sup>2</sup>, p = 0.006) with similar calcific scores (p = 0.614). Women had greater fibrotic scores than men

in bicuspid (224[181-307] versus 169[109- 247] mm<sup>3</sup>/cm<sup>2</sup>; p = 0.042) but not tricuspid valves (p = 0.232). Men had greater calcific scores than women in both bicuspid (203[124-355] versus 130[70-182] mm<sup>3</sup>/cm<sup>2</sup>; p = 0.008) and tricuspid (177[136-249] versus 100[62-150] mm<sup>3</sup>/cm<sup>2</sup>; p = 0.004) valves. Among both valve types, women had greater fibro-calcific ratio compared to men (tricuspid 1.86[0.94-2.56] versus 0.86[0.54-1.24], p = 0.001 and bicuspid 1.78[1.21-2.90] versus 0.74[0.44-1.53], p = 0.001).

### **Conclusions**

In severe aortic stenosis, bicuspid valves have proportionately more fibrosis than tricuspid valves, especially in women.

### **26. Women with atrial fibrillation more likely to develop dementia**

New data suggest a significantly stronger link in women compared with men between atrial fibrillation (AF) and mild cognitive impairment (MCI) and dementia.

“Our findings imply that women with AF may be at higher risk for MCI and dementia with potentially more rapid disease progression from normal cognition to MCI or dementia than women without AF or men with and without AF,” wrote authors of a new study led by Kathryn A. Wood, PhD, RN, Neil Hodgson Woodruff School of Nursing at Emory University in Atlanta.

The findings were published online in [Alzheimer’s & Dementia](#).

Researchers used the National Alzheimer’s Coordinating Center data with 43,630 patients and analyzed sex differences between men and women with AF and their performance on neuropsychological tests and cognitive disease progression.



### **Higher odds of dementia, MCI in women**

According to the paper, AF is associated with higher odds of dementia (odds ratio [OR], 3.00; 95% confidence interval [CI], 1.22-7.37) in women and MCI in women (OR, 3.43; 95% CI, 1.55-7.55) compared with men.

Women with AF and normal cognition at baseline had a higher risk of disease progression (hazard ratio [HR], 1.26; 95% CI, 1.06-1.50) from normal to MCI and from MCI to vascular dementia (HR, 3.27; 95% CI, 1.89-5.65) than that of men with AF or men and women without AF.

AF is a major public health problem linked with stroke and heart failure, and is an independent risk factor of increased mortality. It is associated with higher risk of cognitive impairment and dementia independent of stroke history.

### **Cognitive screening for AF patients**

The authors wrote that cognitive screening, especially in women, should be part of yearly cardiology visits for patients with AF to help identify early those at highest risk for cognitive disease.

T. Jared Bunch, MD, professor of medicine in the division of cardiovascular medicine at University of Utah in Salt Lake City, said in an interview, “We have learned that how we treat atrial fibrillation can influence risk.”

First, he said, outcomes, including brain health, are better when rhythm control approaches are used within the first year of diagnosis.

“Restoring a normal heart rhythm improves brain perfusion and cognitive function. Next, aggressive rhythm control – such as catheter ablation – is associated with much lower long-term risks of dementia in the [patients]. Finally, early and effective use of anticoagulation in patients with atrial fibrillation lowers risk of stroke, dementia, and cognitive decline.”

## **Several factors unknown**

Dr. Bunch said there are some unknowns in the study, such as how long patients were in atrial fibrillation.

He said one way to address the inequities is to refer women earlier as women are often referred later in disease to specialty care, which can have consequences.

He said it is not known how many people underwent early and effective rhythm control.

“Women also are less likely to receive catheter ablation, a cardioversion, or be placed on antiarrhythmic drugs,” said Dr. Bunch, who was not part of the study. “These also represent potential opportunities to improve outcomes by treating the rhythm in a similar and aggressive manner in both men and women.”

Also unknown is how many people were on effective oral anticoagulation, Dr. Bunch noted.

The study importantly highlights a significant problem surrounding the care of women with AF, he said, but there are strategies to improve outcomes.

In addition to earlier screening and referral for women, providers should recognize that men and women may present differently with different AF symptoms. He added that physicians should offer catheter ablation, the most effective treatment, equally to men and women who are candidates.

In all people, he said, it’s important “to start anticoagulation very early in the disease to lower the risk of micro- and macrothrombotic events that lead to poor brain health and function.”