News in August 2023

1. Sex Differences in Mild to Moderate Aortic Stenosis Progression

Study Questions:

Are there any sex differences in the progression and outcomes of mild to moderate native aortic stenosis (AS)?

Methods:

The authors performed a retrospective single-center cohort study of patients with mild to moderate native tricuspid AS from the echocardiographic database of the Cleveland Clinic health system between 2008–2016 and followed until 2018. Patients aged ≥60 years with mild or moderate native AS, defined as aortic valve area (AVA) between 1.0–2.0 cm^2 on index echocardiogram, were identified. Baseline patient characteristics including demographics, comorbidities, medications, laboratory data, and echocardiographic data were obtained from the electronic medical records based on comprehensive chart review of data. Echocardiographic and Doppler measurements were obtained by an experienced sonographer and adjudicated by an expert board-certified echocardiogram reader according to established guidelines. The primary outcome was all-cause mortality, aortic valve replacement (AVR), and the secondary outcome was disease progression assessed by annualized changes in echocardiographic parameters.

Results:

Among 2,549 included patients, the mean age was 74 years, 42.5% were female, and 89.8% were white. The median duration of follow-up was 5.7 years. In baseline characteristics, relative to females, males had a higher prevalence of chronic comorbidities as in higher hyperlipidemia (78.6% vs. 74.3%, $p = 0.011$), atrial fibrillation (29.9% vs. 25.2%, $p = 0.009$), and coronary artery disease (CAD) (57.2% vs. 36.1%, $p < 0.001$). There was no difference in all-cause mortality between sexes irrespective of age, baseline disease severity, progression to severe AS, and receipt of AVR.

In secondary outcomes, males had a significantly faster disease progression represented by greater increases in the median of annualized change in mean gradient (2.10 vs. 1.15 mm Hg/year, respectively, $p < 0.001$), maximum transvalvular velocity (0.42 vs. 0.28 m/s/year), and left ventricular (LV) end-diastolic diameters (0.15 vs. 0.048 mm/$m^{2.7}$/year) ($p = 0.014$).

Further, females had differences in LV remodeling and filling pressures and had significantly higher LV ejection fraction (LVEF), E/e', right ventricular systolic pressure, and LV septum thickness over time both in the overall population and in the 1:1 propensity-matched group of patients on follow-up echocardiograms compared to males.

Conclusions:

In patients with native mild to moderate AS, males have higher burden of chronic conditions including CAD and hypertension. Males and females have distinct clinical and echocardiographic profiles of LV remodeling in response to chronic pressure overload, with females having a higher likelihood of concentric hypertrophy, higher LVEF, filling pressures, and LV septum thickness over time on follow-up echocardiograms compared to males. Males have higher mean gradient and faster progression of disease severity.

Perspective:

Recent genetic, molecular, and clinical data have identified sex-based differences in clinical characteristics at time of diagnosis, symptom onset and severity, valvular progression and the concomitant degree of ventricular adaptation and remodeling, and clinical outcomes in patients with AS. This is a large, real-world sample of a patient population followed for a long time. The study focuses on distinct sex-specific differences in disease progression. The recent guidelines have noted sex-specific criteria for aortic calcification based on calcium.

The study adds to the growing body of literature of distinct LV remodeling and clinical progression between the two sexes. The observed differences in AS progression between sexes in this study suggest variations in underlying mechanisms of ventricular adaptation to pressure overload via varying

phenotypic pathways of LV remodeling and valvular degeneration. These differences are clinically relevant and play into progression to symptomatic disease between the two sexes.

2. Patients With High BMI May Experience More Cardiotoxicity

A recent study out of the North-East region of Colombia found that patients with a high body mass index (BMI) treated for breast cancer may experience more cardiotoxicity during chemotherapy. The study will be presented during ACC Latin America 2023 Together with Asociación Costarricense de Cardiología, held Aug 11-12 in San Jose, Costa Rica.

Ivetteh Gaibor Santos, MD, et al., used an anonymized database of breast cancer patients who started chemotherapy with doxorubicin or trastuzumab between January and December 2021 to examine the impact of BMI on heart health during chemotherapy. The analysis only included patients who had a baseline echocardiogram and at least one follow-up echocardiogram. The database also recorded sociodemographic, oncological, cardiovascular and echocardiographic variables.

The study cohort included 67 patients, with an average age of 55 years old and mean BMI of 26.18 kg/m². Baseline characteristics of the study cohort included obesity (20.9%), hypertension (14.93%) and Type 2 diabetes (13.43%). All the patients had a normal left ventricular ejection fraction before starting chemotherapy.

Results found the prevalence of cardiotoxicity was 11.94%. A body mass index of 25 and above (overweight/obesity) was the only predisposing risk factor for developing this adverse effect. According to the study authors, early diagnosis of cardiotoxicity and related factors is vital to allow treating clinicians to reduce adverse outcomes.

“Addressing obesity in cancer patients before starting chemotherapy as well as considering the potential risk for cardiotoxicity requires a comprehensive approach,” Gaibor Santos said. “Some strategies clinicians can consider include pre-treatment assessment, lifestyle interventions and cardiovascular risk management. It is important to note that these strategies should be tailored to each patient’s specific needs and in accordance with current evidence-based guidelines.”

ACC Latin America 2023 will bring together global experts to discuss, share and critique the latest in cardiovascular prevention to improve the heart health and care in patients throughout Latin America and the Caribbean. Other clinical cases and poster presentations include:

- Chemotherapy-Induced Cardiotoxicity in Patients with Breast Cancer – A Single Center Registry
- CHAGA-Check – An AI-Based Diagnosis and Early Treatment Model for Chagas Disease in Underserved Communities: A Cost-Effectiveness Feasibility Study
- Clinical Implications of Cardiac Magnetic Resonance Findings Among Women in Developing Nations
- Prevalence of Self-Reported Acquired Cardiovascular Disease and Risk Factors Among Adolescents and Young Adults in Low- and Middle-Income Countries

3. Sex-Specific Effects of BP-Lowering Pharmacotherapy for the Prevention of CVD

BACKGROUND

Whether the relative effects of blood pressure (BP)-lowering treatment on cardiovascular outcomes differ by sex, particularly when BP is not substantially elevated, has been uncertain.

METHODS

We conducted an individual participant-level data meta-analysis of randomized controlled trials of pharmacological BP lowering. We pooled the data and categorized participants by sex, systolic BP categories in 10-mm Hg increments from <120 to ≥170 mm Hg, and age categories spanning from <55 to ≥85 years. We used fixed-effect 1-stage individual participant-level data meta-analyses and applied Cox proportional hazard models, stratified by trial, to analyze the data.

RESULTS

We included data from 51 randomized controlled trials involving 358 635 (42% women) participants. Over 4.2 years of median follow-up, a 5-mm Hg reduction in systolic BP decreased the risk of major cardiovascular events both in women and men (hazard ratio [95% CI], 0.92 [0.89-0.95] for women and 0.90 [0.88-0.93] for men; *P* for interaction, 1). There was no evidence for heterogeneity of relative treatment effects by sex for the major cardiovascular disease, its components, or across the different baseline BP categories (all *P* for interaction, ≥0.57). The effects in women and men were consistent across age categories and the types of antihypertensive medications (all *P* for interaction, ≥0.14).

CONCLUSIONS

The effects of BP reduction were similar in women and men across all BP and age categories at randomization and with no evidence to suggest that drug classes had differing effects by sex. This study does not substantiate sex-based differences in BP-lowering treatment.

4. **High prevalence of pre-eclampsia in women with coarctation of the aorta**

Introduction

Women with repaired coarctation of the aorta (CoA) are expected to reach fertile age due to improvements in early surgical repair, surgical techniques,

management of arterial hypertension, and other complications.[1,2] Pregnant women with repaired CoA are considered to have an intermediate risk of maternal mortality and moderate-to-severe risk of morbidity, with a previously reported event rate of 10–19% during pregnancy. Women with repaired CoA correspond to modified World Health Organization (mWHO) Classes II and III, while women with unrepaired severe CoA are classified as mWHO Class IV.[3] The complication rates have varied due to reports on different endpoints and variable proportions of pregnant women with repaired vs. unrepaired CoA.[4–7] Despite improvements in survival for patients with CoA, cardiac complication rates are relatively high, with re-coarctation in 34%, aortic aneurysms in 18%, chronic hypertension in 32%, and a 10-fold increase in cerebrovascular events compared to healthy controls.[2] Coarctation of the aorta is associated with progressive arterial stiffening, and the timing of surgery does not affect this systemic vascular remodelling.[8]

Women with structural heart disease such as CoA may have a higher risk of developing pre-eclampsia, as these disorders have shared risk factors such as chronic hypertension. Maternal mortality is higher in patients with a combination of heart disease and pre-eclampsia than in pregnant women without cardiovascular disease. The recent European Society of Cardiology (ESC) Registry of Pregnancy and Cardiac disease (ROPAC) report found maternal mortality of up to 3.5% of heart disease patients with pre-eclampsia. All pre-eclampsia-related deaths occurred post-partum, most associated with heart failure.[9] Prevention of pre-eclampsia is gaining increased awareness, and the prescription of low-dose acetylsalicylic acid (ASA) to women with a high risk of pre-eclampsia in Norway may explain the decline in the prevalence in the general population in the last decade. Low-dose ASA is used to prevent cardiovascular diseases in high-risk populations, but women of reproductive age are rarely prescribed ASA for this indication.[10]

Contemporary data from the pregnancy history and its outcome are needed for an updated cardiovascular risk assessment in women with CoA. Our primary aim was to report on pregnancy outcomes in women with CoA in

Norway. The secondary objective was to explore any associations between CoA and pre-eclampsia.

Methods

Study design and population

We performed a single-centre, retrospective study in pregnant women with CoA. By review of the database at the National Unit for Pregnancy and Heart Disease at Oslo University Hospital—Rikshospitalet in Norway—every pregnancy in women with CoA from 2008 to 2021 was included. Inclusion criteria were repaired and unrepaired CoA and pregnancy. A team of cardiologists dedicated to grown-ups with congenital heart disease (CHD) performed pregnancy risk stratification in all women with CoA and consequently counselled those with the lowest mWHO risk to delivery at their local hospital. Women with a higher mWHO risk were advised to have follow-up and delivery at our tertiary centre.

Clinical registrations

Clinical data were obtained from a review of the database at the National Unit for Pregnancy and Heart Disease at Oslo University Hospital—Rikshospitalet. Characteristics of the CoA, the status of the aortic valve, associated congenital heart defects, medication, and occupational status were registered. The last follow-up consultation, including clinical assessment and echocardiography, was recorded and included in the statistical analysis for the follow-up data.

Maternal cardiovascular endpoints

The cardiovascular endpoints registered through pregnancy until follow-up were hospitalization for cardiovascular reasons, heart failure, arrhythmias, thromboembolic events, aortic dissection, acute coronary syndrome, and death. A major adverse cardiac event[11] was defined as a composite outcome of these endpoints. Native and recurrent CoA and associated cardiac defects

were diagnosed by echocardiography, magnetic resonance imaging (MRI), computed tomography (CT), or cardiac catheterization.

Obstetric and neonatal endpoints

Obstetric data from the mother and the neonate were obtained through a review of obstetrical charts, including blood pressure (BP) every trimester, pre-delivery, and post-partum before discharge from the birth clinic. Obstetric endpoints were pregnancy-induced hypertension, pre-eclampsia, or *haemolysis, elevated liver enzymes, low platelets* (HELLP) syndrome, and post-partum haemorrhage. Mode of delivery was registered, as spontaneous or assisted vaginal delivery, defined as the vaginal birth performed with the help of forceps or a vacuum device. A caesarean section was registered as planned or emergency. Neonatal endpoints were perinatal mortality >24 weeks of gestation, infant death (<6 months), pre-term delivery (<37 weeks of gestational age), low Apgar score (<7) at 1 and 5 min, and low birth weight.

Data handling

Women with repaired and unrepaired CoA were included in the study. Retrospective systolic BP (SBP) and diastolic BP (DBP) trajectories collected from the obstetric record throughout pregnancy were analysed. Hypertensive disorders of pregnancy were defined as pregnancy-induced hypertension, pre-eclampsia, or HELLP syndrome, according to the 2018 International Society for the Study of Hypertension in Pregnancy (ISSHP) statement.12 Pre-eclampsia was defined as hypertension after 20 weeks' gestation accompanied by proteinuria and/or evidence of maternal acute kidney injury, liver dysfunction, neurological features, haemolysis or thrombocytopenia, or foetal growth restriction. We performed a subgroup analysis on the women who fulfilled the definition of pre-eclampsia. Postpartum haemorrhage was defined as >1000 mL blood loss or signs of hypovolaemia within 24 h after birth, regardless of the mode of delivery.13 Birth weight was classified as low when <2500 g.14 The non-invasive SBP gradient between the upper and lower extremities (ULE) was calculated to identify patients with a peak-to-peak

gradient ≥20 mmHg, requiring increased vigilance and additional examinations on the status of the CoA situation.15 Dilatation of the ascending aorta was defined as an ascending aortic diameter >40 mm.

Statistical analysis

Baseline characteristics and outcomes were compared in women with and without pre-eclampsia. Data are presented as mean ± standard deviations (SD) for normally distributed continuous variables. The median and range are presented for continuous and not normally distributed variables. Linearity was assessed by partial regression plots. Normality was assessed by Q-Q plot. Comparisons of continuous variables between groups were made by unpaired Student's *t*-tests, while the Mann–Whitney *U* test was applied to compare continuous variables with skewed distribution between groups. A comparison of categorical variables was made using Pearson's x^2 or Fisher's exact test, as appropriate. Mixed model analysis was applied to analyse repeated measurements on retrospective BP data. To investigate the strength of association with pre-eclampsia, the relevant variables with significant associations in univariate analyses and clinical variables known to affect pre-eclampsia were selected for multiple regression analysis. The likelihood ratio test was used to determine the statistical significance of the independent variables. A $P < 0.05$ was considered statistically significant for all statistical tests. Data analysis was performed using STATA Standard Edition Version 17 (StataCorp LLC, Texas, USA).

Patient and public involvement

This research was approved by the Data Protection Officer (PVO) at Oslo University Hospital to safeguard the research participant's privacy, interest, and rights. Individual patients' consent was waived.

Results

Seventy-six women with CoA and 87 pregnancies were included in the study. Twelve of the women conducted delivery at their respective local hospitals.

Baseline characteristics before pregnancy are presented in *Table 1*, comparing the CoA patients with and without pre-eclampsia. Surgical characteristics of the primary repair of the CoA is presented in the table as Supplementary material.

Seventy-two (95%) women had an initial repair of CoA before their first completed pregnancy. Four (5%) patients underwent uncomplicated pregnancy with unrepaired CoA. Re-operation was performed within the first 2 years of life in 17 (22%) patients. All patients were diagnosed by computed tomography or MRI scan, and all women had repeated echocardiography during clinical follow-up before and after pregnancy. Four (5%) patients underwent pregnancy with an unrepaired CoA without major cardiac events (MACE). Risk factors for pre-eclampsia, such as parity, age, body mass index (BMI), and chronic hypertension, were comparable in the CoA patients who developed pre-eclampsia vs. those women without pre-eclampsia. The two groups were comparable regarding cardiac function expressed by ejection fraction (EF) and valvular function. In the total study population, patients with bicuspid aortic valve (BAV) (n = 38, 49%) had significantly more aortic regurgitation (25% vs. 12% $P < 0.001$), aortic valve stenosis (16% vs. 4%, $P = 0.004$), and larger diameter of ascending aorta on echocardiography before pregnancy (33 ± 4 mm vs. 28 ± 6 mm; $P = 0.002$) compared to women without BAV. Twenty-five (33%) women had intervention due to re-coarctation before pregnancy, either by open surgery (n = 17) or percutaneous balloon angioplasty (n = 8).

Maternal cardiovascular outcome during pregnancy

The occurrence of hypertensive disorders of pregnancy in 87 pregnancies in women with CoA is shown in *Figure 1*. Sixteen pregnancies (18%) in 15 women (20%) were complicated by pre-eclampsia. Five women (7%) with hypertension before pregnancy had superimposed pre-eclampsia. All the pre-eclamptic patients had proteinuria upon pre-eclampsia diagnosis. There were no cases of eclampsia or HELLP. One patient had pre-eclampsia with early onset, i.e. before the 34th week of gestation, and delivered by emergency caesarean

section. One patient had a reoccurrence of pre-eclampsia in her second pregnancy without any other peri-partum or foetal complications. Five (7%) women were diagnosed with pregnancy-induced hypertension.

All three (4%) women who experienced MACE had pre-pregnancy hypertension. In patients with BAV, 16 (21%) had hypertension before pregnancy ($P = 0.01$).

A low-dose ASA was initiated in 22 (25%) pregnancies during the first trimester, and logistic regression analysis for pre-eclampsia showed an odds ratio (OR) 0.22 [95% confidence interval (CI) 0.10–0.41; $P = 0.021$]. Chronic hypertension and co-existing heart disease were identified as risk factors for pre-eclampsia and an indication for initiation of ASA in these patients.

There were no maternal deaths. There were no aortic dissections, acute coronary syndromes, cerebrovascular events, or interventions due to CoA in pregnancy. During pregnancy, only three (4%) patients had hospital admissions due to MACE. These three patients had repaired CoA, combined with a severe CHD: Patient 1 due to progression of mitral regurgitation and pulmonary hypertension (in the third trimester), Patient 2 due to dyspnoea and worsening of systolic and diastolic function (in the third trimester), and Patient 3 due to progressive symptoms of supraventricular tachycardia (in the second trimester). Patients 1 and 2 had combined congenital heart defects (mitral insufficiency and pulmonary hypertension; ventricular septal defect and aortic stenosis) and had EF < 50% on hospital admission. There were no cases of new onset of heart failure during pregnancy.

Obstetric and neonatal outcomes

Obstetric and neonatal data are shown in *Table 2*. During the study period, two women had a second pregnancy. These two pregnancies were not included in the analysis, because outcome data were not available at the time of registration.

The differences in BP between the measurements from the first trimester through pregnancy and post-partum were highly significant in the pre-eclamptic group. The stepwise and pairwise comparison of SBP throughout pregnancy is reported in *Table 3*. Repeated measures of retrospectively collected SBP and DBP during the first, second, and third trimesters, pre-delivery, and post-delivery before discharge from the maternal ward are shown in *Figure 2*. Blood pressure measurements before discharge showed higher SBP (131 ± 9 vs. 123 ± 11; $P = 0.119$) and DBP (75 ± 8 vs. 69 ± 12; $P = 0.051$) in the pre-eclamptic women compared to those without pre-eclampsia. All women with pre-eclampsia (without pre-pregnancy hypertension) ($n = 10$, 13%) were treated with calcium blocker and beta-blocker before delivery.

Caesarean section was performed in 25% of the deliveries, of which 3% were emergency caesarean sections. Preterm delivery was more common in women with pre-eclampsia. In women with pre-eclampsia, the Apgar score at 1 min was significantly lower compared to patients without pre-eclampsia ($P = 0.047$); the Apgar score at 5 min was comparable between the groups ($P = 0.651$). Four neonates had congenital heart defects: three atrial septal defects and one persistent ductus arteriosus. There were no perinatal or infant deaths.

Predictors of pre-eclampsia

Multi-variable logistic regression analysis for predictors of pre-eclampsia is displayed in *Figure 3*. Maternal age at first pregnancy (OR 1.37; 95% CI 1.09–1.71; $P = 0.006$), BMI before first pregnancy (OR 1.77; 95% CI 1.28–2.44; $P = 0.009$), and using ASA from the first trimester (OR 0.22; 95% CI 0.10–0.41) were statistically significantly associated with pre-eclampsia. The logistic regression model was statistically significant with a likelihood ratio of $x^2 = 73.75$ ($P = 0.000$). Assessing the goodness of fit of the model, the likelihood ratio pseudo-$R^2 = 0.749$.

Maternal cardiovascular function after pregnancy

Data from follow-up of patients with CoA after pregnancy are shown in *Table 4*.

After a median follow-up of 8 years since the first completed pregnancy, five (7%) women had undergone surgery or balloon angioplasty for re-coarctation, one (1%) woman for ascending aortic aneurysm, one (1%) for descending aortic aneurysm, and one (1%) for aortic valvular stenosis. Two patients had primary repair of their CoA after the first pregnancy, one had balloon angioplasty, and one had surgical repair with aortic valve replacement. Five (6%) women showed an increase in the diameter of the ascending aorta above 40 mm, one requiring surgery due to the dilatation. The two patients with combined congenital heart defects (mitral stenosis and pulmonary hypertension; ventricular septal defect and aortic stenosis) had reduced systolic and diastolic ventricular function, which did not worsen after pregnancy.

At follow-up, 29 (38%) women were on anti-hypertensive medication, compared to 22% before pregnancy. The mean SBP (119 mmHg ± 7 vs. 115 mmHg ± 11; $P = 0.119$) and DBP (71 mmHg ± 10 vs. 67 mmHg ± 8; $P = 0.639$) were comparable in CoA patients treated for hypertension vs. patients without anti-hypertensive medication. However, for patients with pre-eclampsia, the mean SBP was 9% higher ($P = 0.013$), and the mean DBP was 16% higher ($P = 0.001$) compared to patients without pre-eclampsia. Seven (9%) women had an ULE SBP gradient >20 mmHg. These women are followed-up with repeated echocardiography and MRI to evaluate the need for re-intervention of re-coarctation. At follow-up, the cardiac index was 10% lower in women with previous pre-eclampsia ($P = 0.052$).

Discussion

This report from the National Unit for Pregnancy and Heart Disease in Norway finds a prevalence of 20% of pre-eclampsia in women with CoA. This

prevalence is much higher than in the healthy pregnant population[16] and substantially higher than in the last report on pregnancy outcomes in women with CoA from the ROPAC study. Age and BMI were significant predictors of pre-eclampsia. Aspirin decreased the OR and seemed to have a protective effect on the development of pre-eclampsia. We found low rates of MACE, in line with recent reports.[17]

Pre-eclampsia

The prevalence of 20% pre-eclampsia observed in our cohort is significantly higher than the 2.6% reported in the recent ROPAC study.[17] It is also higher than the prevalence observed in a recent, large population-based cohort study from Staff *et al.* using data from the Medical Birth Registry of Norway.[16] In previous studies, hypertensive disorders have been reported as the most frequent pregnancy complication in women with repaired CoA, with rates between 14% and 20%.[4,6] In the largest retrospective study to date period, Krieger *et al.*[18] found pre-eclampsia rates of 7% in their large CoA cohort. In the prospective study by Siegmund *et al.*[7] of 49 women with CoA, the authors found no difference in hypertensive disorder between healthy controls and women with CoA.

Our cohort of CoA women with and without pre-eclampsia had comparable BPs before pregnancy and in the first trimester. The pre-eclamptic women showed a significant increase in SBP and DBP in the second and third trimesters compared to women without pre-eclampsia, as expected from the commonly described clinical presentation of pre-eclampsia.[19] They were closely followed with repeated BP measurements and adjustment of anti-hypertensive treatment with beta-blockers and calcium blockers. At follow-up, 8 years after the first pregnancy, the SBP and the DBP were higher in the pre-eclamptic group than in patients without previous pre-eclampsia. The use of anti-hypertensive treatment was higher at follow-up (32%) compared to during pregnancy (12%).

Contrary to our findings in the CoA cohort, the prevalence of pre-eclampsia in the Norwegian population has decreased from 4.3% to 2.7% over the last two decades. An increase in aspirin prescriptions among pregnant women and an overall increase in labour inductions are observed. This suggests that clinical interventions may partly explain the observed reduction in prevalence in the general population.16 Lower average BP and improved health in the general population may also explain the decline in prevalence.20

Large population-based cohort studies have established the association between PE and cardiovascular disease21 and the shared common risk factors (e.g. hypertension, obesity, and diabetes).22 Studies indicate that cardiovascular dysfunction precedes pre-eclampsia, predominates in the clinical syndrome, and persists post-partum. Both endothelial dysfunction and cardiac changes have been documented from the clinical presentation of pre-eclampsia and beyond pregnancy. The most common cardiac changes include altered left ventricular (LV) geometry with hypertrophy, global diastolic dysfunction, and, in more severe cases, LV systolic dysfunction.23,24 The endothelial dysfunction observed in early- and late-onset pre-eclampsia25 exists beyond pre-eclamptic pregnancies.26,27 Coarctation of the aorta is also associated with endothelial dysfunction, expressed in reduced vascular reactivity, and associated with hypertension and increased LV mass.28

A recent meta-analysis could demonstrate a weak association between maternal CHD and pre-eclampsia, except for aortic stenosis and pulmonary atresia.29 Their meta-regression analysis for CoA of pre-eclampsia on a total of 13 studies, including eclampsia and HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) in women with CHD, could not find a significant correlation ($P = 0.094$), though with heterogeneity in variability across studies considered to be moderate ($I^2 = 69\%$).30 The rate of PE, eclampsia, and HELLP syndrome taken together was 4.3% (in a total of 33 included studies). None of the included studies presented data separately for early- and late-onset PE, so whether CHD specifically predisposes women to

early- or late-onset PE could not be evaluated. Women with CHD included in the meta-analyses may have received ASA, but these data were unavailable.

One-fourth of the pregnancies in our study received low-dose ASA from the first trimester throughout pregnancy. The prophylactic effects of ASA have shown a modest ability to reduce the risk of developing pre-eclampsia and its sequelae.31 The Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial showed that ASA initiated in the first trimester to a high-risk population identified by first-trimester screening test could reduce the incidence of early-onset pre-eclampsia by 62%.32 In the ROPAC report on pregnancy outcomes in women with CoA, ASA was only used in 5.9% of pregnancies. It was not associated with a lower incidence of hypertensive disorders (OR 1.1).17 Prescription of ASA for high-risk pregnancies has recently been incorporated in American,33 British,34 and Norwegian guidelines.35

With the high prevalence of pre-eclampsia in our study cohort, the risk of pre-eclampsia and hence the indication for ASA could be underestimated in certain CoA patients. Pre-existing cardiovascular disease, including CHD (and associated lesions like a BAV), may confer a higher risk of pre-eclampsia than previously assumed. Future prospective studies should explore this relationship.

Maternal mortality

There were no maternal deaths in our cohort. The worldwide prospective ROPAC data from the ESC EURObservational Research Program on pregnancies in women with CoA (n = 303 pregnancies) from 2007 to 2018 reported no maternal mortality.17 This is in line with our results.

The most extensive retrospective data collection on American women with CoA (n = 697 deliveries) from 1998 to 2007 by Krieger *et al.*18 included maternal deaths in their composite adverse cardiovascular outcome, preventing direct comparison on mortality to our results.

Major adverse cardiac events

We had a MACE rate of 5% during the first pregnancy in the CoA cohort, which is lower than the predicted 10–19% event rate for patients in the mWHO risk Classes II and III.[3] All patients developing MACE had an additional cardiac condition to the CoA (mitral stenosis and pulmonary hypertension; ventricular septal defect and aortic stenosis). Despite ongoing medical treatment, these patients had clinical worsening leading up to the cardiac event and hospitalization. Feared complications like aortic dissections, coronary artery dissections, cerebrovascular events, or endocarditis did not occur during pregnancy or post-partum in this cohort. Major cardiac event rates in the reports from the ROPAC cohort (4.3%) and Krieger *et al.* (5%) were also low (4.3%). The ROPAC report found predictors of MACE to be pre-pregnancy signs of heart failure, LVEF < 40%, NYHA Class > 1, and the use of cardiac medication before pregnancy.

Concerning risk, most of the patients in our cohort will be stratified into mWHO Risk Class II, corresponding to a small increased risk of maternal mortality or moderate increase in morbidity.

Obstetrical and neonatal outcome

Two-thirds of the patients in our cohort had a vaginal delivery, and 22% of the women had a caesarean section. This is substantially lower than the observed caesarean section rate of 50% in the ROPAC report on women with structural cardiac disease. Planned caesarean sections in uneventful pregnancies for patients with structural heart disease offer no maternal advantage, while they may increase adverse foetal outcomes.[36,37]

Evidence from randomized controlled trials that can inform practice regarding planned caesarean section vs. vaginal delivery for women with pre-eclampsia is lacking.[38]

There was a non-significant lower birth weight in infants of mothers treated with beta-blockers. This contrasts a recent study by Sørbye *et al.*[39], reporting

a five-fold increased risk of delivering a small-for-gestational-age infant in women with heart disease treated with a high dose of beta-blocker, and a two-fold increased risk among those treated with a low dose, showing an apparent 'dose–response' relation. We found a low rate (3%) of CHD in the offspring, although the recurrence rate is reported to be up to 6.5% for non-syndromic maternal CoA.40 Our data are in line with the recent ROPAC report.17

Strengths and limitations of the study

The strength of this registry study was the complete inclusion of the CoA cohort for the pre-pregnancy and follow-up data. The study had no patients lost to follow-up. From the patient register, we had access to validated information on exposure and outcome variables on all the CoA patients after pregnancy.

In Norway, adults with CHD (ACHD), including patients with CoA, have regular follow-up by ACHD cardiologists at the outpatient clinic. This provides a complete overview of the ACHD population. The pregnant women with ACHD are referred to the National Unit for Pregnancy and Heart Disease for evaluation and follow-up.

Contrary to multi-centre registries, this may perhaps explain the difference in prevalence of pre-eclampsia from our study to previous reports. However, contemporary prospective studies should be performed to confirm our results. A dedicated team of cardiologists, obstetricians, anaesthesiologists, midwives, and nurses standardized the patient follow-up and treatment during the study period. Pre-pregnancy counselling and risk stratification, essential for fertile women with CoA to conduct a safe pregnancy, were performed according to current guidelines, illustrated in *Figures 4* and *5*.

This study has limitations due to the nature of the retrospective design and the observational data from a single centre. Inherent to our study design is selection bias to the results. Also, the number of events in our data is low. This should be considered in interpreting the study results. To draw any causal inference between pre-eclampsia and cardiovascular disease and CoA

is challenging. Reports from considerable observational data across the past two decades can only show strong associations between pre-eclampsia and cardiovascular outcomes.

Conclusion

In our study, we found a high prevalence of pre-eclampsia in women with CoA. Pre-eclampsia is a cardiovascular risk factor, and ASA should be considered for women with CoA as prevention for pre-eclampsia. Our results show that pregnancy in women with repaired CoA is safe, but vigilance to the presentation of pre-eclampsia is critical to avoid severe peri-partum complications. Over one-fourth of the CoA patients received anti-hypertensive treatment after pregnancy. Long-term follow-up, with targeted anti-hypertensive treatment and lifestyle modifications, is mandatory to prevent cardiovascular disease.

5. Study Finds No Increased Risk of CVD Years After Infertility Therapies

he use of assisted reproductive technologies (ART) is not associated with an increased intermediate-term risk of CVD, according to the large multination Nordic ART study.

While some nonsignificant trends were seen depending on the method of ART used, there were no differences in incident CVD risk at a median of 11 years in the overall cohort of women who used ART versus those who did not.

“These findings may be reassuring to the increasing number of individuals who require assistance from ART to conceive,” say Maria C. Magnus, PhD (Norwegian Institute of Public Health, Oslo), and colleagues in their paper published online August 9, 2023, in *JAMA Cardiology*.

Many women with infertility have polycystic ovary syndrome (PCOS) or endometriosis, both of which have been linked to a higher risk of CVD, making it important to understand if the technologies themselves contribute further risk, Magnus and colleagues note. Potential ways this could occur are either

through ovarian hyperstimulation that results in a prothrombotic state and/or endothelial injury, or by causing accelerated biological aging. Moreover, prior analyses had delivered mixed results as to possible harms of ART.

In an accompanying editorial, Stephanie A. Fisher, MD, MPH (Northwestern University Feinberg School of Medicine, Chicago, IL), and colleagues say the data are much needed and consistent with a 2017 meta-analysis that included over 1.4 million women and found no significant difference in rates of cardiovascular events between those who did and did not undergo fertility treatment, although an earlier large US analysis had pointed to increased risk.

In the same way that we ask people about hormonal contraception or breast or ovarian cancer, we should be asking about infertility treatment. Stephanie A. Fisher

"I think one of the main concerns with the current literature that we have on ART and long-term cardiovascular disease risk is just that we're missing those data," Fisher told TCTMD. "This dataset is very robust and has one of the longest follow-ups that we have in any cohort to be able to better address this question among people seeking to conceive."

Nordic ART Population

The study included 2,496,441 individuals who gave birth in Denmark (1994-2014), Finland (1990-2014), Norway (1984-2015), and Sweden (1985-2015). Overall, 4% had received ART. In women with no ART, the mean age was 29 years, while in the ART group it was 33.8 years. In addition to being older, women with ART had a lower parity and were less likely to use tobacco.

Overall, incident rates of any CVD over follow-up that ranged from 5 to 18 years across the studies was not significantly different between those who did and didn't use any form of ART: 188 vs 152 events per 100,000 person-years (adjusted HR 0.97; 95% CI 0.91-1.02). Similarly, no differences were seen

between women in the ART versus no ART groups in rates of ischemic heart disease, cerebrovascular disease, stroke, cardiomyopathy, heart failure, pulmonary embolism, or deep vein thrombosis. The ART group did, however, show a lower risk of MI compared with the non-ART group (HR 0.80; 95% CI 0.65-0.99).

The main findings did not change after adjustment for multiple gestation, pregnancy complications, tobacco use, BMI, or educational level. Individual analyses by type of ART showed a trend for an increased risk of stroke in those who underwent frozen embryo transfers compared with women with no ART (HR 1.59; 95% CI 1.11-2.26), with no evidence of a similar difference between those who underwent fresh embryo transfers and those with no ART (HR 0.91; 95% CI 0.80-1.05). The association between frozen embryo transfer and stroke risk persisted after further adjustment for pregnancy complications.

Magnus and colleagues say a heightened risk with frozen transfers "might reflect an increased risk of hypertensive disorders of pregnancy, since preeclampsia is associated with future risk of stroke." Embryo selection and epigenetic changes associated with freezing or thawing, also could be potential explanations, they add. Importantly, however, it also could reflect a greater severity of female or male fertility problems since having a frozen transfer often occurs after an unsuccessful fresh embryo transfer.

Investigators also saw a significantly lower risk for any CVD with in vitro fertilization (IVF) involving intracytoplasmic sperm injection (ICSI) versus no ART (HR 0.83; 95% CI 0.74-0.94). Here, the researchers say their suspicion is that "women who used IVF with ICSI did not have fertility problems themselves, as this reflects largely fertility problems among their partners [and] they might be reproductively healthier, which again might be reflected in their decreased risk of CVD."

That uncertainty is another ongoing challenge in this type of research, Fisher noted.

“We need to tease out whether it's ART alone or developing hypertension during pregnancy. This study alone is not able to address that, and neither is a lot of our literature,” she said.

The need for long-term follow-up of women who have undergone fertility treatments also raises issues of how or if they are being tracked over time. Data from the Women’s Health Initiative suggest that infertility may be associated with subsequent risk for heart failure with preserved ejection fraction, but that many women don’t share infertility history with providers because they either aren’t asked about it or don’t think it’s relevant.

“An egg retrieval should be documented as a surgical procedure as part of the medical history,” Fisher noted. “Getting into the details of ART type is more challenging, but in the same way that we ask people about hormonal contraception or breast or ovarian cancer, we should be asking about infertility treatment [because] it’s an important exposure that we should be capturing in order to better study long-term outcomes.”

While Fisher and colleagues say the generalizability of the Nordic cohort to other more-heterogeneous populations like the United States is somewhat limited, as is the ability to replicate this type of data in a US population.

“We don't have the robust databases like Canada or many of these European countries where they're able to look at hundreds of thousands or even millions of individuals like they did in this study,” Fisher told TCTMD. “I think it's a reflection of the very fractured nature of our healthcare system that we don't have the ability to access these mass reporting systems.”

6. **Socioeconomic disparities in peripartum cardiomyopathy**

Peripartum cardiomyopathy (PPCM) is an uncommon complication that occurs towards the end of pregnancy or in the months following delivery. The hallmark of PPCM is heart failure and left ventricular dysfunction, where no other cause of heart failure is identified. Although almost half of the women

with PPCM will experience a mild course with full recovery, others can present with severe depression of left ventricular function and cardiogenic shock requiring mechanical circulatory support or cardiac transplantation.1 Hence, PPCM carries a high mortality rate ranging from 4% to 11% in young women leading to significant distress and hardship to society.2

The factors that affect prognosis in PPCM include age, multi-parity, hypertension, pre-eclampsia as well as racial and socioeconomic disparities.3 There is a striking variation in the frequency of PPCM around the world ranging from 1 in 4000 live births in the Western world to 1 in 100 lives births in Africa.1 The extreme difference in incidence is most likely secondary to different population demographics and different awareness levels. However, the geographic variation and resulting socioeconomic disparities may have contributed to this wide range of incidence. The extent to which socioeconomic parameters contribute to worse outcomes in PCCM has been gaining interest after multiple studies have linked social vulnerability to worse cardiovascular outcomes in heart failure and coronary artery disease.

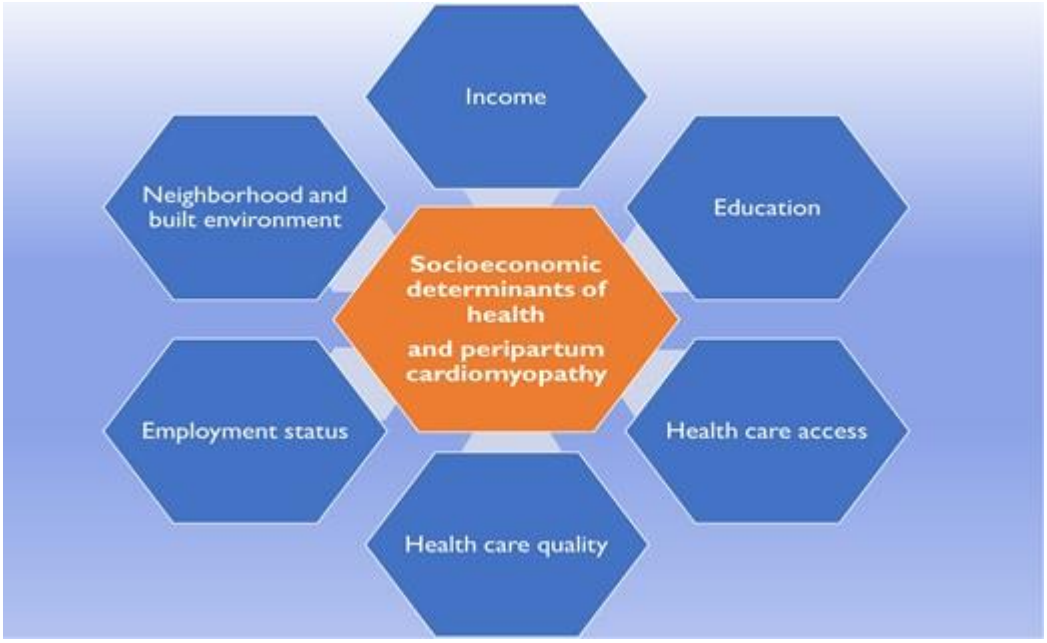
The multinational European Society of Cardiology EURObservational Research Programme (ESC EORP) registry included over 700 women with PPCM from 49 countries showing that PPCM occurs in women from different ethnic backgrounds in all continents.4 The registry showed several notable geographical findings. Patients with PPCM in Europe were older than in other regions, while African women were the youngest. Women from the Middle East had the highest prevalence of diabetes and multiparity. Pre-eclampsia and hypertension were more prevalent in the Asia-Pacific region. In addition, the delay between symptom onset and the diagnosis was greatest in Africa and shortest in Europe. All-cause mortality at 6 months was higher in the Middle East (10%) and least frequently in Europe (4%). Left ventricular recovery occurred most frequently in women in the Asia-Pacific region (62%) and least frequently in those in the Middle East (25%). This registry highlighted the different demographics and outcomes in women with PPCM in different regions. Given the multiple confounding factors, a sub-study of the registry

investigated the characteristics and outcomes of women with PPCM according to individual-level sociodemographic factors utilizing personal income and educational attainment. Additionally, country-specific sociodemographic factors as reflected by the Gini coefficient, health expenditure, and human developmental index were evaluated. The study showed higher maternal and neonatal deaths in patients from countries with low health expenditures. Moreover, women with low income and lower levels of education had worse outcomes, irrespective of the country.3

It is well established that African ancestry is a strong risk factor for PPCM.1 A study reported that African-American women had a 15.7-fold higher relative risk of PPCM than non–African-Americans.5 Moreover, a US study that included 220 individuals showed that women of African ancestry were diagnosed with PPCM later in the post-partum period and at a younger age in comparison to non–African-ancestry women. Additionally, women of African ancestry were also more likely to worsen after initial diagnosis, have longer recovery time, and have higher recovery failure despite adequate treatment.6 While genetic differences party accounts for the worse outcomes in African ancestry, it has been speculated that socioeconomic disparities may account for some of the differences. Later, the same group demonstrated that lower socio-economic status was associated with sustained cardiac dysfunction which was defined as persistent left ventricular ejection fraction <50%, left ventricular assist device placement, transplant, or death.7 Another retrospective study that included 95 women with PPCM showed that patients who lived in communities with greater social vulnerability had a worse composite outcome of ejection fraction <30%, death, intensive care unit admission, left ventricular assist device or implantable cardioverter defibrillator placement, or transplant.8 Similarly, in a propensity matched study that included more than 2 million pre-eclampsia/eclampsia delivery hospitalizations showed higher incidence of PPCM, heart failure, and pulmonary oedema in White women with low income in comparison to White women with high income. Among Black women, low income was associated with a trend for higher incidence of PPCM; however, the difference was not

statistically significant (*P* value: 0.07).9 Furthermore, another study that included 145 individuals showed that women with PPCM had lower socio-economic scores in comparison to their race-matched controls.10

In conclusion, women with social vulnerabilities are more likely to develop severe forms of PPCM and sustain worse cardiovascular outcomes. Maximal efforts that include better patient education, improving access to health care, allocation of adequate health resources, and increased awareness among healthcare providers should be sustained to close the gap.



7. **Reflections After ACC.23 From the Council of the Women in Cardiology**

Introduction

The American College of Cardiology (ACC) Women in Cardiology (WIC) Leadership Council hosted several sessions in the WIC Lounge at the ACC.23 Annual Meeting with the intention of collaborative discussion toward widening the pathway and furthering the opportunities to include WIC. Some sessions focused on empowering women, supporting leadership and career advancement, protecting women's health, and addressing the barriers in the work environment. Among the ACC members, the United States and

international physician WIC members constitute approximately 15% according to the ACC member data in 2023. The purpose of this article is to share the efforts of WIC at the ACC.23 meeting and the actionable items discussed at these sessions toward a leveled playground for WIC and to create a safe space for open dialogue (**Figure 1**).

Women in Cardiology: Issues to Ideas.

ACC Women Leaders Session

Moderator: Sharonne Hayes, MD

Panel and Speakers: Athena Poppas, MD, Claire Duvernoy, MD, Mary Norine Walsh, MD, Dipti Itchhaporia, MD

The WIC Section meeting launched with an empowering session with the ACC-WIC leaders. Even though women are underrepresented in leadership roles in cardiology, we were honored by the presence and willingness of the esteemed leaders who shared their experiences and pearls. The panel included 3 ACC past presidents and a board of trustees member. Their inspiring pathways showcased that women have made strides in ACC leadership. They shared their barriers with imposter syndrome, importance of self-advocating, and their success and failures. This session offered an honest discussion with

potential solutions to overcome obstacles and how to be an effective leader by choosing professionalism, hard work, patience, and resilience.

Ideas discussed

- Collective leadership that champions other WIC (and men)
- Building trust, fostering individual confidence, honesty, and integrity
- Defining clear goals with delegation
- Leveraging team members' talents
- Being a good listener
- Creating a culture of "feedback loops" in conversations
- Developing a culture of adaptability and accountability and not losing the sight of the "big picture"
- Acting against implicit biases that undermine leadership expansion
- Diversifying teams to encourage varied ideas and talents

Where Are the Women?

Chair: Kamala Tamirisa, MD

Panel and Speakers: Doreen Defaria Yeh, MD, Janet K. Han, MD, Martha Gulati, MD, C. Michael Gibson, MD

Despite the number of WIC increasing over time, they are less likely to be full professors, receive research funding, have a registered clinical trial, and they are underrepresented on the editorial boards of cardiovascular journals. Women hold few departmental leadership positions in medicine, even in female-dominated specialties. Women authors of manuscripts studying these disparities presented their work and stimulated a lively discussion of where we are and what the future holds. Dr. Defaria Yeh highlighted the sex

differences in faculty rank among academic cardiologists in the United States; Dr. Gulati offered data on gender differences in guideline authorships in the United States, Canada, and Europe; Dr. Gibson offered solutions to end gender inequality in clinical trial leadership; and Dr. Han discussed pathways to promote diversity and in inclusion in cardiovascular societies. An engaging discussion left the audience with some potential solutions as we look at the future.

Potential solutions

- Deliberate sponsorship of women
- Intentional recruitment of WIC talent
- Engaging male allies
- Increasing efforts to empower WIC researchers with designated and paid time for research
- Offering support and resources
- Awarding grants to women

These initiatives need broad, intentional, and collective efforts at institutional, individual, and organizational levels.

Increase WIC in Research

Chairs: Kristen Brown, MD, Jennifer Rymer, MD

Panel and Speakers: Roxana Mehran, MD, Puja Mehta, MD, LaPrincess Cerise Brewer, MD, Tracy Wang, MD, Daniel R. Anderson, MD, Jennifer Rymer, MD

Research for academic advancement, personal satisfaction, and the science community's betterment remains outside easy reach for many WIC today. The reasons for this sex disparity have been proposed and investigated, including

the underrepresentation of women in the field and the lower likelihood of women to gain leadership positions,[1] the lesser compensation,[2] and underrepresentation in randomized trials.[3]

The benefits of having women researchers in original research within the cardiology field are endless. Research studies conducted by women primary investigators are more likely to include sex-based analyses. Models should be implemented to exemplify an accessible-distributed research team model to help increase women physician representation and improve the academic women cardiologists' landscape. Dr. Mehran explained the landscape of WIC in research and her pathway to becoming a successful clinical trialist, Dr. Mehta described how to launch a pathway in research at the training and early career stages, Dr. Brewer shared how to become funded by creating community-based research and to find ways to diversify the teams, Dr. Wang highlighted her experiences as a successful trialist, Dr. Anderson explained how to be an ally, and Dr. Rymer offered research resources available to WIC.

Highlighted solutions

- Building early mentorship programs for clinician scientists
- Incorporating basic, translational, community-based, and clinical outcomes research into early education
- Sponsoring industry-supported research
- Creating courses and support for effective grant writing

Conversations Around Pregnancy Issues

Chairs: Sarah Rosanel MD, Estefania Oliveros MD

Panel and Speakers: Jennifer Co-Vu, MD, Gina Lundberg, MD, Kamala P. Tamirisa, MD, Garima Sharma, MD, Toniya Singh, MD, L. Zahedi-Spung, MD

The decision by the Supreme Court in the case of Dobbs v Jackson and its impact on maternal health, including maternal and fetal cardiovascular health, was discussed. The American College of Obstetrics and Gynecology (ACOG) condemned this ruling, and currently the treatment of patients is dependent on the state governments' rulings and terms. ACC also released a statement sharing similar sentiments with ACOG and that the College is deeply concerned about the potential implications of the Supreme Court decision regarding Roe v Wade on the ability of patients and clinicians to engage in shared discussions about maternal health, given the alarming maternal health crisis in the United States. This session included a talk by a well-recognized maternal and fetal medicine/high-risk obstetric specialist, Dr. Zahedi-Spung, who educated the audience about the legal influence on clinical practice patterns across academic and private practice entities. The cardiologists' professional role in the care of mothers and fetuses with heart disease, and how the legislation will affect our careers professionally, were addressed.

Key points

- Know your state laws
- Advocate for improvement in laws in states where there are bans
- Monitor morbidity and mortality boards
- Watch for impact on women at the greatest risk for complications resulting from social determinants of health such as low income and limited education

Flexible Schedules in Cardiology Careers

Chairs: Gina Lundberg, MD, Toniya Singh

Panelists: Mary Norine Walsh, MD, Claire Duvernoy, MD, Sharonne Hayes, MD

A career is “an occupation undertaken for a significant period of a person's life and with opportunities for progress.: Therefore, throughout an individual’s life and career, many events, planned or unplanned, may occur that require flexibility, alterations, and changes from the system and the individual to accommodate a cardiologist’s career. There may also be additional roles or responsibilities that the cardiologist decides to embark upon, creating the need to adjust work-related duties or compensation models. The recent 2022 ACC Health Policy Statement on Career Flexibility in Cardiology provided the mainstem for the discussion.[4] This statement is extensive and all-encompassing, with issues including parental leave, medical leave, changes in career, activities outside career, aging, and retirement. This statement affects fellows, early career, mid-career, and advanced career physicians of both sexes and all areas of cardiology careers, from academic to private practice, research, and industry.

Key purposes of the statement

- All cardiologists would benefit from flexibility in work hours and responsibilities
- Help retain cardiologists who need time off temporarily and increase their longevity
- Provide flexibility to address the projected shortage of cardiologists

Future

The ACC WIC Leadership Council objectives are to increase WIC in training, in the workforce, and in leadership while enhancing professionalism. WIC supports women of all ages, stages, and subspecialties. Fostering work-life integration as well as providing mentoring and networking opportunities while promoting personal well-being are essential. This year’s sessions were heavily attended not only by the WIC section members but also by male allies, ACC leadership, and other section members. By sharing the key points of these sessions, we hope to help highlight the ACC’s and ACC WIC’s efforts toward

equity in cardiology and serve as a resource for our members, medical societies, and institutions.

8. **Disparities in Guideline-Recommended Statin Use for the Prevention of ASCVD by Race, Ethnicity, and Gender**

BACKGROUND

Although statins are a class I recommendation for prevention of atherosclerotic cardiovascular disease and its complications, their use is suboptimal. Differential underuse may mediate disparities in cardiovascular health for systematically marginalized persons.

OBJECTIVE

To estimate disparities in statin use by race-ethnicity-gender and to determine whether these potential disparities are explained by medical appropriateness of therapy and structural factors.

DESIGN

Cross-sectional analysis.

SETTING

National Health and Nutrition Examination Survey from 2015 to 2020.

PARTICIPANTS

Persons eligible for statin therapy based on 2013 and 2018 American College of Cardiology/American Heart Association blood cholesterol guidelines.

MEASUREMENTS

The independent variable was race-ethnicity-gender. The outcome of interest was use of a statin. Using the Institute of Medicine framework for examining unequal treatment, we calculated adjusted prevalence ratios (aPRs) to estimate disparities in statin use adjusted for age, disease severity, access to health care, and socioeconomic status relative to non-Hispanic White men.

RESULTS

For primary prevention, we identified a lower prevalence of statin use that was not explained by measurable differences in disease severity or structural factors among non-Hispanic Black men (aPR, 0.73 [95% CI, 0.59 to 0.88]) and non-Mexican Hispanic women (aPR, 0.74 [CI, 0.53 to 0.95]). For secondary prevention, we identified a lower prevalence of statin use that was not explained by measurable differences in disease severity or structural factors for non-Hispanic Black men (aPR, 0.81 [CI, 0.64 to 0.97]), other/multiracial men (aPR, 0.58 [CI, 0.20 to 0.97]), Mexican American women (aPR, 0.36 [CI, 0.10 to 0.61]), non-Mexican Hispanic women (aPR, 0.57 [CI, 0.33 to 0.82), non-Hispanic White women (aPR, 0.69 [CI, 0.56 to 0.83]), and non-Hispanic Black women (aPR, 0.75 [CI, 0.57 to 0.92]).

LIMITATION

Cross-sectional data; lack of geographic, language, or statin-dose data.

CONCLUSION

Statin use disparities for several race-ethnicity-gender groups are not explained by measurable differences in medical appropriateness of therapy, access to health care, and socioeconomic status. These residual disparities may be partially mediated by unobserved processes that contribute to health inequity, including bias, stereotyping, and mistrust.

9. **Prepregnancy Factors Explored in Racial Disparity in Preterm Birth**

Prepregnancy factors related to socioeconomic status and cardiovascular health are associated with racial differences in the rates of preterm birth (PTB), according to a research letter published online Aug. 6 in the *American Journal of Preventive Medicine*.

Priya M. Mehta, M.D., from the Northwestern University Feinberg School of Medicine in Chicago, and colleagues examined the relative contributions of prepregnancy risk factors toward racial differences in contemporary PTB rates. Data were included for 509,890 live births to non-Hispanic Black individuals and 1,790,350 live births to non-Hispanic White individuals.

The researchers found that PTB occurred in 116.3 and 72.3 per 1,000 live births among non-Hispanic Black and non-Hispanic White individuals, respectively (racial difference of 44.0 per 1,000 live births). At the time of delivery, non-Hispanic Black versus White individuals were younger; more likely to have prepregnancy hypertension, diabetes, and obesity; and less likely to smoke, have a college education, or have private insurance. A statistically significant portion of the difference in PTB rates was explained by both prepregnancy cardiovascular risk factors and socioeconomic factors (7.8 and 21.3 percent, respectively). PTB rates would be 3.4 and 9.4 per 1,000 live births lower, respectively, if non-Hispanic Blacks had the same average distribution of prepregnancy cardiovascular risk factors and socioeconomic factors as non-Hispanic Whites.

"Preterm birth is the starting point for racial differences across the life course, not just in childhood," coauthor Sadiya Khan, M.D., also of the Northwestern University Feinberg School of Medicine, said in a statement.

10. **Impact of Pregnancy on the Natural History of Women With Hypertrophic Cardiomyopathy**

AIM

Whether pregnancy is a modifier of the long-term course and outcome of women with hypertrophic cardiomyopathy (HCM) is unknown. We assessed the association of pregnancy with long-term outcomes in HCM women.

METHODS

Retrospective evaluation of women with HCM from 1970 to 2021. Only women with pregnancy-related information (pregnancy present or absent) and a follow-up period lasting ≥1 year were included. The peripartum period was defined as -1 to 6 months after delivery. The primary endpoint was a composite for major adverse cardiovascular events (MACE: cardiovascular death, sudden cardiac death, appropriate defibrillator shock and heart failure [HF] progression).

RESULTS

Overall, 379 (58%) women were included. There were 432 pregnancies in 242 (63%) patients. In 29 (7.6%) cases, pregnancies (n=39) occurred after HCM diagnosis. Among these, three carrying likely pathogenic sarcomeric variants suffered MACEs in the peripartum period. At 10±9 years follow-up, age at diagnosis (hazard Ratio [HR]: 1.034, 95% confidence interval [C.I.]: 1.018-1.050, p<0.001) and NYHA Class (II vs I: HR 1.944, 95% C.I. 0.896-4.218; III vs I: HR 5.291, 95% C.I. 2.392-11.705, p<0.001) were associated with MACE. Conversely, pregnancy was associated with reduced risk (HR 0.605; 95% C.I. 0.380-0.963, p=0.034). Among women with pregnancy, multiple occurrences did not modify risk.

CONCLUSIONS

Pregnancy is not a modifier of long-term outcome in women with HCM, and mostly occurs before a cardiac diagnosis. Most patients tolerate pregnancy well and do not show a survival disadvantage compared to women without. Pregnancy should not be discouraged, except in the presence of severe HF symptoms or high-risk features.

11. **FLAVOUR Data Suggest Sex Differences in FFR- and IVUS-Guided PCI Strategies**

The use of fractional flow reserve (FFR) led to a lower percutaneous coronary intervention (PCI) rate but had a similar prognostic value compared to intravascular ultrasound (IVUS) in both women and men, while women with intermediate stenosis had more favorable outcomes than men despite receiving fewer interventions, according to secondary analysis data from the FLAVOUR trial.

The study was reported Sunday at the European Society of Cardiology (ESC) Congress 2023 and published simultaneously in *JACC: Cardiovascular Interventions*.

Speaking at ESC 2023 in Amsterdam, study co-author Xinyang Hu, MD, PhD, from The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China, noted that recent trial data suggested an FFR-guided PCI strategy was non-inferior to an IVUS-guided one with respect to the composite of death from any cause, myocardial infarction (MI), and any revascularization at 2 years with fewer stents.

However, the authors, led by Jinlong Zhang, MD, PhD, and Jun Jiang, MD, PhD, also of The Second Affiliated Hospital of Zhejiang University School of Medicine, noted that the impact of sex on these outcomes remains unclear – adding that women have different phenotypes of coronary artery disease (CAD) "with respect to its pathogenesis, anatomical and functional characteristics, clinical presentation, and prognosis."

"Therefore, FFR and IVUS might play different roles in decision-making for the entire revascularization process and even post-procedural management, leading to different PCI rates and clinical outcomes in women and men," said the authors. "However, the impact of sex differences on the treatment and outcome based on physiology- or imaging-guided revascularization strategy is yet to be elucidated."

Trial setup

The FLAVOUR trial was an investigator-initiated, prospective, multinational, randomized controlled trial that compared FFR- and IVUS-guided PCI strategies in patients with intermediate stenosis deemed eligible for PCI based on visual estimation by angiography. Patients were randomized in a 1-to-1 fashion to undergo an FFR- or IVUS-guided PCI with a second-generation drug-eluting stent.

"In our study, patients were divided into two groups according to treatment: patients who underwent PCI (PCI group), and deferral of PCI with medical treatment (deferral group)," noted the authors, adding that the team then investigated the effect of sex on the treatment and clinical outcomes according to the randomly allocated FFR- or IVUS-guided PCI strategy.

Sex differences

They reported that out of 1,619 patients, 29.8% were women. Compared to men, women were older (67.8 years vs. 63.9 years; p<0.001), less commonly smokers (1.2% vs. 26.4%, p<0.001) and had a higher prevalence of hypertension (73.0% vs. 65.7%; p=0.005), noted the team.

Women were found to have similar mean percent diameter stenosis by visual estimation (61.7 vs. 61.9; p=0.636); however, they were found to show a lower severity of percent diameter stenosis by quantitative coronary analysis (55.9 vs. 57.1; p=0.016).

Furthermore, compared with men, women had a smaller mean minimal lumen area (MLA, 3.3 mm^2 vs. 3.5 mm^2, p=0.022), a smaller mean plaque burden (68.2% vs. 70.9%; p=0.001), a less severe mean area stenosis (69.0% vs. 72.0%, p<0.001), and a higher FFR (0.85 vs. 0.82; p<0.001), said the authors.

Women also had a lower PCI rate (40.8% vs. 47.9%; p=0.008), which was mainly driven by patients undergoing FFR-guided PCI (25.0% vs. 36.8%; p<0.001) but not by those undergoing IVUS-guided PCI (58.4% vs. 59.3%; p=0.867), the authors said, adding that among the entire population, women also had a lower rate of target vessel failure (TVF) at 24 months than men (2.4% vs. 4.5%; hazard ratio [HR] 1.93; 95% confidence interval [CI] 1.03 – 3.62; p=0.040).

“When the patients were divided according to the treatment type, women showed a lower event rate than men in the deferral group (1.7% vs. 5.2%; HR 3.18; 95% CI 1.23 –8.22; p=0.017), but not in the PCI group (3.4% vs. 3.7%; HR 1.12; 95% CI 0.48 – 2.62; p=0.792),” reported the team, noting that in in multivariate regression analyses, sex was an independent predictor of TVF in overall patients (adjusted HR 1.96; 95% CI 1.04 – 3.73; p=0.039) and in the deferral group (adjusted HR 3.70; 95% CI 1.44 – 9.50; p=0.007).

However, in both women and men, there were no differences in the rates of TVF (women, FFR vs. IVUS: 2.2% vs. 2.5%; HR 0.90; 95% CI 0.29 – 2.78; p=0.852; men, FFR vs. IVUS: 4.8% vs. 4.1%; HR 1.18; 95% CI 0.68 – 2.03; p=0.549) or in patient-reported clinical outcomes between the FFR- and IVUS-guided strategies

“In cases of intermediate stenosis, incorporating FFR- or IVUS-guided decision-making alongside angiography may help avoid systematic bias in assessing lesion severity in women, particularly in those who underwent invasive angiography as the initial test for CAD investigation,” concluded the authors, adding that women had more favorable outcomes than men with fewer revascularizations.

“The use of FFR led to a lower PCI rate but similar prognostic value compared to IVUS in both women and men,” they added, noting that further studies are needed to clarify if the findings remain consistent when incorporating a comprehensive assessment with physiologic or imaging factors, alongside local hemodynamics, microvascular function, qualitative plaque characteristics, and 3D lumen and plaque distribution.

12. **Breastfeeding for at Least Six Months Aids Maternal Cardiovascular Factors**

Breastfeeding for at least six months may reduce some maternal cardiovascular risk factors in women three years postpartum, according to a study published online July 19 in the *International Breastfeeding Journal*.

Maleesa M. Pathirana, Ph.D., from University of Adelaide in Australia, and colleagues used three-year follow-up data from 160 women-child dyads participating in the Screening Tests to Predict Poor Outcomes of Pregnancy study. Differences in cardiometabolic health were compared between mothers who breastfed for at least six months and their children versus those who did not.

The researchers found that women who breastfed for at least six months had significantly lower maternal body mass index (BMI), systolic blood pressure (BP), diastolic BP, mean arterial pressure, central systolic BP, and central diastolic BP versus those who did not. Results were similar even after adjusting for BMI and socioeconomic index in early pregnancy, prenatal smoking, and maternal age in early pregnancy. Significantly lower maternal systolic and diastolic BPs, serum insulin and triglycerides, and higher high-density lipoprotein cholesterol were seen among women who had one or more pregnancy complications during the index pregnancy (i.e., preeclampsia, gestational hypertension, delivery of a small-for-gestational-age infant, delivery of a preterm infant, and/or gestational diabetes mellitus) and who breastfed for at least six months. Anthropometric and hemodynamic variables were similar among children regardless of breastfeeding duration.

"It may be beneficial to provide interventions that support breastfeeding in disadvantaged women with pregnancy complications to reduce their risk of cardiovascular disease," the authors write.

13. **Sex Differences in Post-Stroke Cognitive Impairment Among Patients With Acute Ischemic Stroke**

BACKGROUND

Poststroke cognitive impairment (PSCI) occurs in about half of stroke survivors. Cumulative evidence indicates that functional outcomes of stroke are worse in women than men. Yet it is unknown whether the occurrence and characteristics of PSCI differ between men and women.

METHODS

Individual patient data from 9 cohorts of patients with ischemic stroke were harmonized and pooled through the Meta-VCI-Map consortium (n=2343, 38% women). We included patients with visible symptomatic infarcts on computed tomography/magnetic resonance imaging and cognitive assessment within 15 months after stroke. PSCI was defined as impairment in ≥1 cognitive domains on neuropsychological assessment. Logistic regression analyses were

performed to compare men to women, adjusted for study cohort, to obtain odds ratios for PSCI and individual cognitive domains. We also explored sensitivity and specificity of cognitive screening tools for detecting PSCI, according to sex (Mini-Mental State Examination, 4 cohorts, n=1814; Montreal Cognitive Assessment, 3 cohorts, n=278).

RESULTS

PSCI was found in 51% of both women and men. Men had a lower risk of impairment of attention and executive functioning (men: odds ratio, 0.76 [95% CI, 0.61-0.96]), and language (men: odds ratio, 0.67 [95% CI, 0.45-0.85]), but a higher risk of verbal memory impairment (men: odds ratio, 1.43 [95% CI, 1.17-1.75]). The sensitivity of Mini-Mental State Examination (<25) for PSCI was higher for women (0.53) than for men (0.27; *P*=0.02), with a lower specificity for women (0.80) than men (0.96; *P*=0.01). Sensitivity and specificity of Montreal Cognitive Assessment (<26.) for PSCI was comparable between women and men (0.91 versus 0.86; *P*=0.62 and 0.29 versus 0.28; *P*=0.86, respectively).

CONCLUSIONS

Sex was not associated with PSCI occurrence but affected domains differed between men and women. The latter may explain why sensitivity of the Mini-Mental State Examination for detecting PSCI was higher in women with a lower specificity compared with men. These sex differences need to be considered when screening for and diagnosing PSCI in clinical practice.

14. **Is female sex impactful in the pathophysiology, presentation, management, and outlook of type A acute aortic dissection?**

Acute aortic dissection (AAD) is the most common acute aortic syndrome. It is a life-threatening condition and surgical emergency associated with high mortality if not treated promptly. While it is well established that cardiovascular disease recognises different pathophysiological pathways between men and women, there is limited evidence of sex differences in AAS, especially in type A AAD. According to a recent synthesis of clinical studies

on gender differences in type A AAD, women were found to have different baseline characteristics, presentation and outcomes, and thus sex should be considered relevant for diagnosis, risk-stratification and management of type A AAD.

15. **Sex differences in type A acute aortic dissection: a systematic review and meta-analysis**

Background

In acute aortic dissection (AAD) sex heterogeneity reports are not exhaustive and in part even conflicting.

Aims

To explore sex differences in clinical features, management, and outcomes among patients with type A AAD.

Methods and results

A systematic review and meta-analysis of the literature were conducted for studies (2004–2022) reporting type A AAD sex differences. Among the 1938 studies retrieved, 16 (16 069 patients, 7142 women, and 8927 men) fulfilled all eligibility criteria. Data were aggregated used the random-effects model as pooled risk ratio and mean difference. Due to information reported by considered manuscripts, analysis were performed only among surgically treated type A AAD patients. At the time of hospital presentation type A AAD women were older than men but had lower body mass index (BMI), body surface area (BSA), and creatinine plasma levels. Active smoking, bicuspid aortic valve, and previous cardiac surgery were less common in women while diabetes mellitus was more frequent. Furthermore, women experienced more frequently pericardial effusion/cardiac tamponade than men. Interestingly, in-hospital surgical mortality did not differ between sexes [risk ratio (RR), 1.02; 95% confidence interval (CI), 0.53–1.99; $P = 0.95$], whereas 5 (RR 0.94; 95% CI: 0.92–0.97; $P < 0.001$) and 10-year survival (RR 0.82; 95% CI: 0.74–0.92; $P = 0.004$) was higher among men. A descriptive analysis of in-hospital outcomes among medically treated type A AAD patients confirmed prohibitive high mortality for both sexes (men 58.6% vs. women 53.8%, $P = 0.59$).

Conclusions

A female sex phenotype appears to be evident in type A AAD implying the need for a personalized management patient approach along with tailored preventive strategies.

16. **Sex differences in type A acute aortic dissection: a systematic review and meta-analysis**

Background

In acute aortic dissection (AAD) sex heterogeneity reports are not exhaustive and in part even conflicting.

Aims

To explore sex differences in clinical features, management, and outcomes among patients with type A AAD.

Methods and results

A systematic review and meta-analysis of the literature were conducted for studies (2004–2022) reporting type A AAD sex differences. Among the 1938 studies retrieved, 16 (16 069 patients, 7142 women, and 8927 men) fulfilled all eligibility criteria. Data were aggregated used the random-effects model as pooled risk ratio and mean difference. Due to information reported by considered manuscripts, analysis were performed only among surgically treated type A AAD patients. At the time of hospital presentation type A AAD women were older than men but had lower body mass index (BMI), body surface area (BSA), and creatinine plasma levels. Active smoking, bicuspid aortic valve, and previous cardiac surgery were less common in women while diabetes mellitus was more frequent. Furthermore, women experienced more frequently pericardial effusion/cardiac tamponade than men. Interestingly, in-hospital surgical mortality did not differ between sexes [risk ratio (RR), 1.02; 95% confidence interval (CI), 0.53–1.99; $P = 0.95$], whereas 5 (RR 0.94; 95% CI: 0.92–0.97; $P < 0.001$) and 10-year survival (RR 0.82; 95% CI: 0.74–0.92; $P = 0.004$) was higher among men. A descriptive analysis of in-hospital outcomes among medically treated type A AAD patients confirmed prohibitive high mortality for both sexes (men 58.6% vs. women 53.8%, $P = 0.59$).

Conclusions

A female sex phenotype appears to be evident in type A AAD implying the need for a personalized management patient approach along with tailored preventive strategies.

17. **Reducing gap in pre-hospital delay between women and men presenting with ST-elevation myocardial infarction**

Aims

This study aimed to analyse changes in pre-hospital delay over time in women and men presenting with ST-elevation myocardial infarction (STEMI) in Switzerland.

Methods and results

AMIS Plus registry data of patients admitted for STEMI between 2002 and 2019 were analysed using multivariable quantile regression including the following covariates: interaction between sex and admission year, age, diabetes, pain at presentation, myocardial infarction (MI) history, heart failure history, hypertension, and renal disease. Among the 15,350 patients included (74.5% men), the median (interquartile range) delay between 2002 and 2019 was 150 (84; 345) min for men and 180 (100; 414) min for women. The unadjusted median pre-hospital delay significantly decreased over time for both sexes but the decreasing trend was stronger for women. Specifically, the unadjusted sex differences in delay decreased from 60 min in 2002 (P = 0.0042) to 40.5 min in 2019 (P = 0.165). The multivariable model revealed a significant interaction between sex and admission year (P = 0.038) indicating that the decrease in delay was stronger for women (−3.3 min per year) than for men (−1.6 min per year) even after adjustment. The adjusted difference between men and women decreased from 26.93 min in 2002 to −1.97 min for women in 2019.

Conclusion

Over two decades, delay between symptom onset and hospital admission in STEMI decreased significantly for men and women. The decline was more

pronounced in women, leading to the sex gap disappearing in the adjusted analysis for 2019.

18. Have we reached equality in pre-hospital management for women and men with STEMI?

The first call to action on sex disparities in cardiology was published in the early nineties.1 Since then, a relatively large amount of data has revealed sex discrepancies ranging from primary prevention to treatment in acute coronary syndrome (ACS), post-myocardial infarction (MI) therapies, rehabilitation, and finally outcomes.2–7

For the current publication 'Reducing gap in pre-hospital delay between women and men presenting with ST-Elevation myocardial infarction',8 Foster et al. analysed data from over 15 000 patients from the Acute Myocardial Infarction (AMIS) Plus registry, which is an ongoing nationwide prospective registry of patients admitted to Swiss hospitals for ACS.9 The focus of their analysis was the difference in pre-hospital delays between women and men with ST-segment elevation MI (STEMI) over time. Delays were adjusted for important covariates such as age, diabetes, presence of chest pain at presentation and history of MI or heart failure among others. Foster et al. point out three main findings. First, over the entire time span (2002–2019), women had significantly longer pre-hospital delays (median of 180 min) compared with men (median of 150 min, unadjusted analysis). Secondly, over the course of those 18 years, the delay was reduced for both sexes but more so for women: The unadjusted differences between men and women decreased from 60 to 40 min with an interaction between sex and admission year of $P = 0.038$ in the multivariable analysis. Third, the adjusted difference in delay between women and men dropped from 27 min in 2002 to minus 2 min in 2019. In other words, at the end of the observation period, no sex difference in pre-hospital delays remained in the adjusted analysis.

The results give hope and Forster et al. are to be commended for their important contribution to the body of research. However, despite the encouraging results, it would be too early to jump to the conclusion that we have reached equality in pre-hospital management for women and men who suffer from a STEMI. First of all, the median unadjusted pre-hospital delay in the year 2019 was still 180 min for women, which is considerably long.[10] Further, several recent analyses on the same topic—albeit though from other countries—have presented less promising results with persistent delays in women from symptom onset to reperfusion.[3,4,7] The current report from Foster et al. analyses the pre-hospital delay in STEMI patients, also known as symptom-do-door time (compared with the hospital delay, known as door-to-device time). However, it does not give any insight on the various time intervals from symptom onset to arrival at the hospital door that add up to the pre-hospital delay (*Figure 1*).

Yet, the devil lies in the details. Most importantly, the duration analysed by Foster et al. entails two large time intervals: One that is dependent on the patient and one that is dependent on the health care system. The first one is the time from symptom onset to the activation of an emergency medical service or another health care professional by the patient or a relative. The second one is the time from the point where a health care professional is activated to the patient's arrival at the hospital door. Given the intriguing data by Foster *et al.*[8] it would be interesting specifically to know which time intervals were disproportionally reduced while others did not change at all.

With this in mind, it becomes obvious that reducing time delays can only be achieved if the different players are targeted. It is well known that both female patients themselves as well as their health care providers consider them to be at low risk for coronary artery disease and, particularly MI.[2] The latter contributes to an unconscious bias in care. Further, it is likely that there is a societal reason for prolonged delays in women: Previous studies have shown that later presentation times were often associated with woman taking care of other people before themselves, such as their husbands, children and grandchildren.[11] Public campaigns therefore aim at increasing the awareness

of cardiovascular disease risk in women and their health care professionals alike. Multiple campaigns such as the worldwide 'Go Red For Women' have been successfully launched. The current report studied the landscape in Switzerland, where the Swiss Heart Foundation started a campaign targeted on heart disease in women as early as 1998, which was intensified in the years 2012 and 2014. The decreasing delays in women presented in this issue might partly be the result of these efforts.

Another way how to address the issue of unconscious sex bias is through the use of objective protocols and checklists. One of the analyses mentioned above has looked at individual time intervals from symptom onset to arrival at the hospital in patients with STEMI (figure) and found that checklist-based steps such as the time from first medical contact to acquisition of an ECG were the only time periods where no delay was seen in women compared to men.7 Another trial has proven that a simple four-step protocol can be highly efficient in diminishing or even abolishing sex discrepancies in female patients with ACS.5

Lastly, there is an unmet need to influence healthcare policies and behaviours through research. Targets should be to gather more data to fully understand the epidemiological, societal, and biological underpinning of sex discrepancies in pre-hospital delays. One of the priorities will be to include more women into cardiovascular research where they have been underrepresented for decades. The 25% women in the AMIS Plus registry fit well into the current landscape with women making up only a quarter of patients in both randomised cardiovascular trials and hospital-based registries.12

In summary, the current analysis by Foster *et al.*8 displays that over 20 years of education and information campaigning can have a positive effect on women's health. However, sex differences are not only driven by health care providers and patients' obvious behaviours but on the contrary, reflect a complex interplay of healthcare and societal constituents, as well as components inherent to the biology of the female sex and gender.13 In this regard, the journey to equality between women and men has only just begun.

19. Association of Radiation Dose to Cardiac Substructures With Major Ischaemic Events Following Breast Cancer Radiotherapy

BACKGROUND AND AIMS

Patients with left-sided breast cancer receive a higher mean heart dose (MHD) after radiotherapy, with subsequent risk of ischaemic heart disease. However, the optimum dosimetric predictor among cardiac substructures has not yet been determined.

METHODS AND RESULTS

This study retrospectively reviewed 2158 women with breast cancer receiving adjuvant radiotherapy. The primary endpoint was a major ischaemic event. The dose-volume parameters of each delineated cardiac substructure were calculated. The risk factors for major ischaemic events and the association between MHD and major ischaemic events were analysed by Cox regression. The optimum dose-volume predictors among cardiac substructures were explored in multivariable models by comparing performance metrics of each model. At a median follow-up of 7.9 years (interquartile range 5.6-10.8 years), 89 patients developed major ischaemic events. The cumulative incidence rate of major ischaemic events was significantly higher in left-sided disease (P = 0.044). Overall, MHD increased the risk of major ischaemic events by 6.2% per Gy (hazard ratio 1.062, 95% confidence interval 1.01-1.12; P = 0.012). The model containing the volume of the left ventricle receiving 25 Gy (LV V25) with the cut-point of 4% presented with the best goodness of fit and discrimination performance in left-sided breast cancer. Age, chronic kidney disease, and hyperlipidaemia were also significant risk factors.

CONCLUSION

Risk of major ischaemic events exist in the era of modern radiotherapy. LV V25 ≥ 4% appeared to be the optimum parameter and was superior to MHD in predicting major ischaemic events. This dose constraint could aid in achieving better heart protection in breast cancer radiotherapy, though a further validation study is warranted.

20. **Study Underscores Geographical and Sex-Based Differences in Global CVD Risk Factors**

The prevalence and impact of the five major cardiovascular risk factors, including body mass index (BMI), systolic blood pressure (SBP), non-HDL-cholesterol (non-HDL-C), current smoking and diabetes, vary by geographical region and sex globally, according to new research presented at ESC Congress 2023 and simultaneously published in the *New England Journal of Medicine*.

The study used individual-level data among 1,518,028 participants from 112 cohort studies conducted in 34 countries and eight geographic regions (North America, Latin America, Western Europe, Eastern Europe and Russia, North Africa and Middle East, sub-Saharan Africa, Asia, and Australia) participating in the Global Cardiovascular Risk Consortium. The median age was 54.4 years and 54.1% were women. Researchers examined associations between the risk factors and incident cardiovascular disease and death from any cause and stratified findings according to geographic region, age and sex. Population-attributable fractions were estimated for the 10-year incidence of cardiovascular disease and 10-year all-cause mortality.

Overall, incident cardiovascular disease occurred in 80,596 participants during a median follow-up of 7.3 years and 177,369 participants died during a median follow-up of 8.7 years. The aggregate global population-attributable fraction of the 10-year incidence of cardiovascular disease across all five risk factors was 57.2% among women and 52.6% among men. The corresponding values for 10-year all-cause mortality were 22.2% and 19.1%, respectively.

Geographically, risk factor levels varied with the highest values for BMI and smoking in Latin America and for SBP and non-HDL-C in Europe. The highest values for diabetes were in North Africa and Middle East. Sex-based

differences were also observed, with smoking and diabetes associated with greater risks for women than men in most geographical regions. The steepest associations between cardiovascular disease and BMI were observed in Latin American women, SBP in North American women, and non-HDL-C in Australian women.

According to **Christina Magnussen, MD**, et al., while all-cause deaths seem to be attributable to five major and potentially modifiable risk factors globally, a substantial proportion of cardiovascular disease and mortality risk remains unexplained. "The present study supports stakeholders on a global and regional scale to tailor geographically adapted and sex-specific initiatives in disease prevention and emphasizes the need for identification of risk factors beyond those used in SCORE risk systems," they said.

21. Maternal CV Risk After Assisted Reproductive Technologies

Study Questions:

Is there an elevated risk of cardiovascular disease (CVD) among individuals who have given birth after assisted reproductive technologies (ART) compared with those who have given birth without ART?

Methods:

A Nordic maternal data linkage registry-based cohort study was conducted using nationwide data from the 1990s to 2015 in Denmark, Finland, Norway, and Sweden. A total of 2,496,441 individuals with a registered delivery in the national birth registries during the study period were included, and 97,474 (4%) of these gave birth after ART. The main exposure was any delivery after using ART, and individuals were classified as exposed from the time of their first delivery from use of ART, including fertilization method (*in vitro* fertilization [IVF] with or without intracytoplasmic sperm injection [ICSI]), or the use of fresh versus frozen embryo transfer, compared with individuals who had not used ART.

The primary outcome was CVD defined as any registration of ischemic heart disease (including myocardial infarction [MI]), cerebrovascular disease (including stroke), cardiomyopathy, heart failure, pulmonary embolism, and deep vein thrombosis (DVT). Clinical characteristics such as age, parity, prepregnancy body mass index, traditional CVD risk factors, and information on adverse pregnancy outcomes such as hypertensive disorders of pregnancy (HDP) and preterm birth were also recorded. Multivariate regression models were created to ascertain the association between ART and CVD after controlling for clinical variables and risk factors. Separate sensitivity analysis was also performed.

Results:

Of 2,496,441 nulliparous women at the start of follow-up without pre-existing CVD, 97,474 (4%) gave birth after ART. The median follow-up time for all individuals was 11 years. The rate of any CVD was 153 per 100,000 person-years. Individuals who gave birth after using ART had no increased risk of CVD (adjusted hazard ratio [AHR], 0.97; 95% confidence interval [CI], 0.91-1.02), with evidence of heterogeneity between the countries (I^2 = 76%; p = 0.01 for heterogeneity).

When examining subgroups of CVD, there was no significant difference between individuals who delivered with and without using ART in the risk of ischemic heart disease, cerebrovascular disease, stroke, cardiomyopathy, heart failure, pulmonary embolism, or DVT. However, there was a lower risk of MI (incidence rates, 14 vs. 12 per 100,000; combined HR, 0.80; 95% CI, 0.65-0.99) among individuals who had used ART.

There was weak evidence that frozen, but not fresh, embryo transfers were associated with an increased risk of stroke (HR, 1.59 [95% CI, 1.11-2.26] for frozen embryo transfer and 0.91 [95% CI, 0.80-1.05] for fresh embryo transfer). The association between frozen embryo transfer and risk of stroke persisted after further adjustment for pregnancy complications (AHR, 1.58 [95% CI, 1.10-1.04]).

Conclusions:

The findings of this large Nordic maternal data linkage study suggest that individuals who gave birth after ART were not at increased risk of CVD over a median follow-up of 11 years compared with those who conceived without ART.

Perspective:

An increasing number of individuals are using ART for conception. A prior meta-analysis showed a higher risk of cerebrovascular disease in individuals undergoing ART as compared to those not. These data are inconsistent and lack the differentiation on method of ART and type of embryo transfer. This large study from the Nordic region with about 11 years of follow-up did not show an increased risk of CVD including stroke, heart failure, and pulmonary embolism or DVT after ART. Some studies have shown an increased risk of HDP in individuals undergoing frozen embryo transfer versus fresh embryo transfer. This study showed weak evidence of increased stroke in frozen transfers as compared to fresh transfers. IVF should be considered an important part of pregnancy and reproductive history and clinicians should focus on optimizing CV risk factors in all pregnant individuals.

22. Sex Differences in Thoracic Aortic Disease and Dissection: *JACC* Review Topic of the Week

Abstract

Despite its higher prevalence among men, women with thoracic aortic aneurysm and dissection (TAAD) have lower rates of treatment and surgical intervention and often have worse outcomes. A growing number of women with TAAD also desire pregnancy, which can be associated with an increased risk of aortic complications. Understanding sex-specific differences in TAAD has the potential to improve care delivery, reduce disparities in treatment, and optimize outcomes for women with TAAD.

Highlights

- Women have a lower prevalence of thoracic aortic disease than men but often have worse outcomes.
- Substantial inequities exist in the management of patients with thoracic aortic disease based on sex, including surgical interventions.
- Sex-specific thresholds for elective intervention of thoracic aortic disease warrant further exploration.

23. Impact of Sex on Cardiovascular Adaptations to Exercise: *JACC* Review Topic of the Week

Abstract

Routine exercise leads to cardiovascular adaptations that differ based on sex. Use of cardiac testing to screen athletes has driven research to define how these sex-based adaptations manifest on the electrocardiogram and cardiac imaging. Importantly, sex-based differences in cardiovascular structure and outcomes in athletes often parallel findings in the general population, underscoring the importance of understanding their mechanisms. Substantial gaps exist in the understanding of why cardiovascular adaptations and outcomes related to exercise differ by sex because of underrepresentation of female participants in research. As female sports participation rates have increased dramatically over several decades, it also remains unknown if differences observed in older athletes reflect biological mechanisms vs less lifetime access to sports in females. In this review, we will assess the effect of sex on cardiovascular adaptations and outcomes related to exercise, identify the impact of sex hormones on exercise performance, and highlight key areas for future research.

Highlights

- Exercise performance, cardiac adaptation, and outcomes of exercise differ based on sex.
- Female sex appears protective against exercise-associated coronary artery calcification, myocardial fibrosis, atrial fibrillation, and sudden cardiac death.
- Greater representation of females in research will improve understanding of the causes of sex-based differences in the effect of exercise on the cardiovascular system.