News in August 2024

1. The Maternal Health Care Crisis: Inequitable and Expensive

Introduction

Cardiovascular disease (CVD) is the leading cause of maternal morbidity and mortality in the United States. Compared to similarly wealthy nations, the United States has the highest maternal mortality, and this continues to rise.1 Moreover, the burden of poor maternal outcomes is disproportionally shared by the most vulnerable. Pregnant women who experience racism, have lower incomes, have limited insurance options/public insurance, live in rural areas, or have poor social support are significantly more likely to have CVD during pregnancy and major adverse cardiovascular events (MACE).2 As these socioeconomic risk factors accumulate, outcomes worsen.

A well-documented irony of the American health care system is that health care costs remain incredibly high, despite poor outcomes. Maternal morbidity and mortality are no exception. Health care for a single normal pregnancy is estimated to cost nearly $19,000 overall.3 With any pregnancy complication, these costs rise substantially due to extended hospitalizations and additional interventions.4 Nonmedical costs, such as lost work productivity, further contribute to the societal costs of maternal morbidity and mortality.

In this issue of JACC: Advances, Williamson et al5 tackle risk factors for adverse cardiovascular outcomes in pregnancy, as well as the increased financial costs of caring for this vulnerable population. This study is one of the larger retrospective studies examining risk factors for adverse cardiovascular outcomes. The authors conducted a retrospective cohort study of pregnant people ages 18 to 50 using data from the National Inpatient Sample Database. Patients included in the CVD cohort had a diagnosis of congenital heart disease, valvular heart disease, cardiomyopathy, or arrhythmias by international classification of disease codes. Notably, aortopathies were not included in this cohort. Pregnant patients with CVD

were overall older, predominately White (with the exception of the subset with cardiomyopathy), and had increased comorbidities, multifetal pregnancies, and cesarean births. MACE were defined as cardiac death, cardiac arrest, heart failure, myocardial infarction, or vascular injury. Malignant arrhythmias were not included as an outcome.

Patients with CVD experienced worse cardiovascular outcomes and had higher obstetric and neonatal complications. Patients with cardiomyopathy and ischemic heart disease had 50-fold and 30-fold greater odds, respectively, of MACE than those without CVD. This study also noted that Black race, low income, and use of public insurance were independently associated with higher rates of MACE, despite the fact that the majority of patients within the study cohort were White. This association further highlights that socioeconomic risk factors alone increase a patient's risk of significant adverse cardiovascular outcomes during pregnancy. The association of MACE with public insurance like Medicaid is particularly interesting, though possible explanations for this are not fully explored in the study. Given that one must have an income at or below 138% of the federal poverty level to qualify for Medicaid, prior poor access to care may lead to adverse sequelae during pregnancy, such as suboptimally controlled diabetes and hypertension. In the Canadian-derived CARPREG II (Cardiac Disease in Pregnancy II) risk index, late prenatal care conferred additional risk for cardiovascular complications.6 Although the study by Williamson et al only examined in-hospital complications, significant maternal morbidity and mortality occur in the postpartum period; therefore, continuation of comprehensive health insurance is essential for decreasing complications and future CVD risk.7

A novel aspect of this study is the analysis of health care costs associated with cardiovascular and obstetric complications at the time of delivery. This is one of the few studies to specifically focus on CVD at the time of delivery. Complications among patients with CVD resulted in a staggering total of $1,075,000,000 in health care expenditures, with $237 million spent on MACE alone. Patients with cardiomyopathy had the worst outcomes, with a length of stay of 5.37 days and an average hospitalization cost of $15,341,

nearly 3 times the cost for patients without CVD. Those with ischemic heart disease followed close behind, with an average hospitalization cost of $11,404. To put this in context, these costs represent a single snapshot at the time of the delivery hospitalization.

The authors should be commended for highlighting the significant economic cost of the delivery hospitalization for patients with CVD. Additional research is needed to determine why these costs are so high, how they can be reduced, and, more importantly, how patient outcomes could be improved. Some areas to explore include whether costs and outcomes vary depending on the size or type of hospital, the presence or absence of a multidisciplinary cardio-obstetrics program, urban vs rural settings, and the type of prenatal counseling and antepartum surveillance. Significant costs come from cesarean deliveries, monitoring in intensive care units, and increased lengths of stay. Many practice patterns are based on local institutional experience and expert opinion; however, increased costs may not translate to improved clinical outcomes. For instance, planned cesarean deliveries are likely overutilized since the majority of patients with CVD can labor safely, even those with cardiomyopathies.8 As the field of cardio-obstetrics continues to evolve, standardization of best practices and the creation of Cardio-Obstetrics Centers of Excellence could reduce unnecessary health care expenditures.

Examining MACE through a health economics lens lends further urgency to the maternal cardiovascular health crisis and offers opportunities for health policy intervention. While Williamson et al focused primarily on health care costs during delivery, this may not reflect the period of highest health care expenditure. Of pregnancy-related deaths, 31% occur during pregnancy, 17% occur on the day of delivery, and the remaining majority occur in the postpartum period.9 Postpartum costs would include rehospitalizations, procedures, and lost wages from extended time away from work. In addition to postpartum costs, we lack data about the costs of managing patients with CVD throughout pregnancy, such as preconception counseling, prenatal care, testing, and management. Frequent clinical surveillance and active management of patients in a cardio-obstetrics program could potentially

reduce the costs of care and MACE at the time of delivery. For example, if patients with cardiomyopathy—who in this cohort were more likely to be Black, a demographic risk factor independently associated with worse cardiovascular outcomes—received more frequent monitoring with visits and echocardiograms throughout their pregnancy, would this decrease the incidence of MACE? If so, would the decrease in MACE-related health care and nonhealth care expenditures offset the increased costs of more frequent monitoring? Further research is needed to better understand the most effective method for monitoring high-risk birthing people during preconception, throughout pregnancy, and in the postpartum period to improve both clinical outcomes and reduce reactionary health care spending.

Pregnancy is a unique opportunity to engage women within the health care system. Given that reproductive rights are no longer nationally guaranteed, more birthing people with high-risk CVD will likely interact with the health care system, and an increased percentage will have one or more socioeconomic risk factors for adverse outcomes. The current study underscores the clinical and economic urgency to determine optimal care and delivery plans for cardio-obstetrics patients. As illustrated in this study, we must continue to strive for more effective methods of reducing adverse maternal outcomes, while also providing more equitable affordable care.

2. Gender and Race Differences in HeartMate3 Left Ventricular Assist Device as a Bridge to Transplantation

Background

Gender and racial disparities exist after left ventricular assist device (LVAD) implantation. Compared with older devices, the HeartMate 3 (HM3) (Abbott Cardiovascular) has demonstrated improved survival. Whether HM3 differentially improves outcomes by gender or race and ethnic groups is unknown.

Objectives

The purpose of this study is to examine differences by gender and race in the use of HM3 among patients listed for heart transplantation (HT) and associated waitlist and post-transplant outcomes.

Methods

The authors examined all patients (20% women, 33% Black) who received LVADs as bridge to transplantation (BTT) between January 2018 and June 2020, in the OPTN (Organ Procurement and Transplantation Network) database. Trends in use of HM3 were evaluated by gender and race. Competing events of death/delisting and transplantation were evaluated using subdistribution hazard models. Post-transplant outcomes were evaluated using multivariate logistic regression adjusted for demographic, clinical, and donor characteristics.

Results

Of 11,524 patients listed for HT during the study period, 955 (8.3%) had HM3 implanted as BTT. Use of HM3 increased for all patients, with no difference in use by gender (P = 0.4) or by race (P = 0.2). Competing risk analysis did not demonstrate differences in transplantation or death/delisting in men compared with women (HT: adjusted HR [aHR]: 0.92 [95% CI: 0.70-1.21]; death/delisting: aHR: 0.91 [95% CI: 0.59-1.42]), although Black patients were transplanted fewer times than White patients (HT: aHR: 0.72 [95% CI: 0.57-0.91], death/delisting: aHR: 1.36 [95% CI: 0.98-1.89]). One-year post-transplant survival was comparable by gender (aHR: 0.52 [95% CI: 0.21-1.70]) and race (aHR: 0.76 [95% CI: 0.34-1.70]), with no differences in rates of stroke, acute rejection, or graft failure.

Conclusions

Use of HM3 among patients listed for HT has increased over time and by gender and race. Black patients with HM3 were less likely to be transplanted

compared with White patients, but there were no differences in post-transplant outcomes between these groups or between men and women.

3. Novel Risk Factors for STEMI Among Young Women: Does Placental Development Offer a Clue?

Adverse pregnancy outcomes (APOs) are increasingly recognized for their contribution to short-term maternal morbidity and mortality, and their longer-term impact on adverse cardiovascular events. The pathophysiology of preeclampsia remains incompletely understood but is thought to occur due to impaired trophoblast invasion and incomplete spiral artery remodeling that result in placental ischemia and thereby an increase in angiogenic markers and vascular endothelial dysfunction.1 Similarly, while diverse etiologies can contribute to intrauterine growth restriction (IUGR), placental insufficiency and malperfusion are key contributors to risk. During pregnancy and the early postpartum period, preterm preeclampsia is a leading cause of adverse maternal and fetal outcomes, including severe maternal hypertension and its downstream complications, pulmonary edema, and diastolic dysfunction.1,2 However, it is also now widely recognized that the effect of APOs extends beyond pregnancy and is associated with a process of accelerated cardiovascular aging.3 As such, APOs are associated with increased risk of diverse cardiovascular complications, particularly among patients aged ≤65.3

In this issue of JACC: Advances, Handmark et al4 extend our understanding beyond association of APOs with incident coronary artery disease (CAD) by investigating severity of myocardial infarctions (MIs) among young women by history of APOs. As hospitalizations for acute MIs have been increasing particularly among younger women, this represents a vulnerable population for whom a better understanding of risk is required.5 Among 8,320 patients age ≤65 years presenting with a first MI in Sweden, the adjusted odds of presenting with a ST-segment myocardial infarction (STEMI) was 40% higher among those with a history of preterm preeclampsia (95% CI: 1.05-1.88) and 30% higher for those with a history of

delivering a small for gestational age (SGA) infant (95% CI: 1.13-1.50) as compared with patients without these APOs. History of term preeclampsia and gestational hypertension has been associated with increased risk of developing CAD but was not associated with increased risk of STEMI in this analysis. While this and other data sets have described a higher burden of comorbid conditions among patients who have experienced APOs as compared with those who have not, increased risk of STEMI persisted after adjustment for body mass index, diabetes, hypertension, smoking status, and treatment for dyslipidemia.

With this analysis, Handmark et al4 demonstrate that APOs are not only associated with an increased risk of any future CAD but also a higher-risk MI presentation. Furthermore, not all APOs confer the same risk for STEMI. This is important to consider with an overarching goal of targeting interventions toward patients who may be at greatest risk. However, as the pathophysiology and exact mechanisms by which APOs confer risk remains incompletely understood, targeted therapies are lacking. Aggressive primary prevention strategies comprise the mainstay of current recommendations, which call for patients to be engaged in longitudinal primary care. However, in a recent analysis of patients in the United States, only 58% with hypertensive disorders of pregnancy engaged in any longitudinal follow-up at 6 months postpartum.6 As such, novel means of educating patients and managing risk factors following APOs are greatly needed. Postpartum transition clinics and virtual care strategies have been proposed to bridge the care gap, but the optimal means of improving access and reducing inequities in care (especially in the context of new caregiving responsibilities) remains an area of active investigation.7 As the current analysis identifies patients with a history of preterm preeclampsia and SGA infants as the highest risk for STEMI, efforts targeted at engaging these highest risk patients may be particularly important.

Traditional cardiovascular risk factors, however, do not account for the totality of risk following APOs. For example, Handmark et al found that

increased risk of STEMI among patients with preterm preeclampsia and SGA persisted in their fully adjusted model, which accounts for differences in comorbid risk. Furthermore, in an analysis restricted to women without hypertensive disorders of pregnancy, Handmark et al found that the association between SGA and future STEMI persisted. As both preterm preeclampsia and IUGR seem to share an underlying mechanism of impaired placental development and consequent endothelial dysfunction, further research into the pathophysiology of this process may ultimately yield targeted therapies for both CAD risk reduction but also improved disease-prevention strategies during pregnancy. At present, low-dose aspirin is recommended for pregnant patients identified as high risk for development of preeclampsia for disease prevention.8 While this strategy has been investigated for IUGR prevention, in the absence of risk factors for preeclampsia it is not currently recommended by the American College of Obstetricians and Gynecologists. Beyond this, evidence-based interventions to reduce the risk of developing either of these APOs are lacking.

Central to better understanding the mechanisms by which APOs increase the risk of future cardiovascular disease is the availability of diverse data sets that capture detailed reproductive histories. Handmark et al were able to leverage the Swedish Medical Birth Register, which afforded an ability to examine diverse APOs more rigorously than other analyses. Many prior observational studies, for example, have grouped all hypertensive disorders of pregnancy together given a lack of granularity in the data, limiting the ability to identify the highest risk patients among this diverse set of disorders. With an increasing recognition of the impact of reproductive risk factors across the lifespan on cardiovascular disease, future cardiovascular studies should intentionally and rigorously capture reproductive risk with sufficient detail to advance our understanding of which patients are at highest risk for adverse outcomes and therefore merit more aggressive preventative care.

4. Sex Differences in Primary Mitral Regurgitation Assessment: Highlighting the Role of Regurgitant Fraction

Introduction

Sex differences, regarding the assessment of mitral regurgitation (MR) severity and cardiac remodeling, have been scarcely addressed and notably absent in current recommendations. In fact, current guidelines propose variable cut-offs that are applied uniformly to both sexes. Studies are scarce on this regard since, in most studies, women have been under-represented and sex has not been taken into account.**1**,**2**

However, recent studies**3**,**4** have suggested that women have a delayed referral for mitral valve intervention, despite more symptomatic, with evidence of more compromised left ventricle (LV) function and likely increase in post-operative risk. This may occur because MR is more frequently diagnosed as moderate in women in spite of symptoms, and additionally, LV dysfunction and dilatation are often misdiagnosed, namely when using values without normalization for body surface area.**5** The assessment of the MR severity in women and the differences between sexes are challenging and need further focused analysis.

For acknowledging differences between sexes in regard to primary MR assessment and its impact on indication for repair, it is crucial not only to identify differences in severity criteria and to define cut-offs for proposing timely management but also to understand the pathophysiology behind those differences.

Women with moderate to severe and severe MR were found to have significantly smaller LV and stroke volumes than men.**6** Also, in patients with organic MR,**7**,**8** women in comparison with men were found to have smaller end-diastolic and end-systolic LV dimensions and lower regurgitant volume. However, these findings were related with the features of advanced disease, such as higher pulmonary pressure, more atrial fibrillation, and heart failure symptoms. The ensuing valve surgery is often delayed by the

classification of MR as moderate as based in conventional cut-offs for regurgitant volumes.

In the current study,**9** the authors aimed to evaluate the phenotypes of primary MR by mitral valve prolapse, according to sexes. Additionally, they aimed comparing men and women regarding the relationship between regurgitation severity and cardiac remodeling with hallmarks of advanced disease such as functional class, LV dilatation, left atrial (LA) dilatation, and pulmonary hypertension. In a large cohort of patients with moderate to severe and severe MR due to valve prolapse referred for MV intervention, the authors analyzed retrospectively data from patients that underwent both echocardiography and cardiovascular magnetic resonance (CMR) for MR severity and cardiac remodeling assessment. In this cohort, women were older than men, had higher NYHA functional class, and larger indexed LA volumes, all hallmarks of clinical severity, despite showing lower MR effective regurgitant orifice area (EROA), regurgitant volumes, as well as ventricular volumes than men. The optimal threshold values for the regurgitant volume and EROA associated with abnormally increased LV size (according to reference) were consistently lower in women than in men. Moreover, for the same regurgitant fraction, regurgitant volumes in women were significantly lower. Regurgitant fraction, in contrast to regurgitant volume, was consistently associated with clinical adverse manifestations such as NYHA functional class III/IV, severe LA dilatation, or pulmonary hypertension, in both sexes. Importantly, optimal cut-offs for regurgitant fraction regarding clinical adverse features were similar in both sexes, while regurgitant volumes were different according to sex even when indexed to body surface area.

A previous study by House et al**10** using CMR described that a regurgitant fraction of 40% correlated with different regurgitant volumes according to sex, with smaller volumes in women, suggesting a gender-independent value for the regurgitant volume in the assessment for MR. In the current study, Altes et al go further, showing that regurgitant fraction had a consistent association with the hallmarks of adverse clinical outcomes with similar

cutoffs in both sexes, in contrast with RV even after indexing to body surface area.

The authors discuss elegantly the findings and raise appropriate hypothesis for justifying the pathophysiology underlying the smaller regurgitant volume in women even when indexed to body surface area. It is conceivable that a more restrictive physiology in women probably related to the smaller heart size and a more advanced myocardial disease, with more fibrosis in advanced age, may have had impact on the LV volumes and cut-offs of severity using this parameter. A recent study on organic MR referred for intervention**11**; women presented evidence of more raised LA stiffness than men, suggesting more advanced cardiac disease. On the other side, indexing the regurgitant volume to the LF total stroke volume seems to provide a more robust index that also takes into account the LV size, providing a unified parameter for severity assessment.

This study represents in advance in knowledge regarding sex-related differences in the clinical and imaging phenotypes of primary MR using state-of-art imaging modalities like CMR and echocardiography. This suggests that using a single EROA or regurgitant volume cut-off values as recommended for grading MR severity in women would place MR severity in the range of moderate, despite the underestimate on the impact of the LV remodeling and delay the referral to mitral valve repair.

Further prospective studies should be undertaken for confirmation of findings, which are promising and with substantial support from an appropriate design and robust methods. First, lower regurgitant volumes and EROA cut-offs for MR severity may be more appropriate from the pathophysiological point of view. Second, regurgitant fraction seems a more robust and independent parameter of severity for both sexes. As also suggested by the authors, this parameter should also be assessed against long-term follow-up for appropriate prognostic purposes and better therapeutic decisions.

Of note, an important issue regards the limitation for echocardiography in challenging cases of primary mitral valve such as late systolic MR or multiple jets in organic MR where concordance between echo and CMR is poor and where regurgitant volume by CMR has been shown to be stronger predictor for mortality or indication for surgery in comparison to echo.**12**

The authors should be congratulated for this nicely designed study that explores the assessment of severity of primary MR in women, a recently identified gap in knowledge that opens new avenues for increased precision in the diagnosis of this valve heart disease.

5. Novel Risk Factors for STEMI Among Young Women: Does Placental Development Offer a Clue?

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With this analysis, Handmark et al4 demonstrate that APOs are not only associated with an increased risk of any future CAD but also a higher-risk MI presentation. Furthermore, not all APOs confer the same risk for STEMI. This is important to consider with an overarching goal of targeting interventions toward patients who may be at greatest risk. However, as the pathophysiology and exact mechanisms by which APOs confer risk remains incompletely understood, targeted therapies are lacking. Aggressive primary prevention strategies comprise the mainstay of current recommendations, which call for patients to be engaged in longitudinal primary care. However, in a recent analysis of patients in the United States, only 58% with hypertensive disorders of pregnancy engaged in any longitudinal follow-up at 6 months postpartum.6 As such, novel means of educating patients and

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6. Age- and Sex-Related Differences in Patients With Wild-Type Transthyretin Amyloidosis: Insights From THAOS

Abstract

Background

Wild-type transthyretin amyloidosis (ATTRwt amyloidosis) is primarily diagnosed in elderly men but diagnoses in younger patients and women have recently increased.

Objectives

The purpose of this study was to examine age- and sex-related differences in patients with ATTRwt amyloidosis enrolled in the THAOS (Transthyretin Amyloidosis Outcomes Survey).

Methods

THAOS was a global, longitudinal, observational survey of patients with transthyretin amyloidosis, including both hereditary and wild-type disease, and asymptomatic carriers of pathogenic transthyretin gene variants. Patient characteristics at enrollment were analyzed by age at enrollment and sex (data cutoff date: August 1, 2022).

Results

Of 1,251 patients with ATTRwt amyloidosis, 13.7%, 49.1%, 34.5%, and 2.8% were aged <70 years, 70 to 79 years, 80 to 89 years, and ≥90 years, respectively. The proportion of women increased with age, from 4.1% in patients aged <70 years to 14.3% in patients aged ≥90 years. In the respective age groups, median time from symptom onset to diagnosis overall (male, female) was 1.7 (1.3, 5.2), 2.0 (2.0, 2.2), 1.8 (1.9, 0.8), and 0.7 (0.6, 2.5) years. A Karnofsky Performance Status score ≤70 was observed in 17.1%, 30.1%, 46.1%, and 44.4% of patients aged <70 years, 70 to 79 years, 80 to 89 years, and ≥90 years, respectively.

Conclusions

In this THAOS analysis of patients with ATTRwt amyloidosis, patients were diagnosed an average of 2 years after symptom onset, with the greatest diagnostic delay in women aged <70 years at 5 years. Patients were predominantly men, but the proportion of women increased with age. A substantial proportion of patients had significant functional impairment regardless of age. (Transthyretin Amyloidosis Outcome Survey [THAOS]; **NCT00628745**)

Introduction

Transthyretin amyloidosis (ATTR amyloidosis) is a progressive disease characterized by the deposition of transthyretin (TTR) amyloid fibrils in the heart, peripheral nerves, and other tissue and organs.**1-3** There are 2 forms of ATTR amyloidosis: hereditary ATTR amyloidosis (ATTRv amyloidosis), in which a pathogenic *TTR* gene variant is present, and wild-type ATTR amyloidosis (ATTRwt amyloidosis), in which no *TTR* gene variant is identified.**2** ATTRwt amyloidosis is primarily characterized by cardiomyopathy,**4** although a mixed phenotype is increasingly described.**5**,**6** ATTRv amyloidosis has a more heterogeneous clinical presentation and can manifest as polyneuropathy, cardiomyopathy, or a mix of both.**5**,**7**

In recent years, there has been a substantial increase in the number of patients diagnosed with ATTR amyloidosis, mostly of the wild-type form, which is now assumed to be the most frequent form of cardiac amyloidosis.**8**,**9** Increased use of noninvasive diagnostic methods and greater clinical suspicion likely contribute to the growing number of diagnoses and the fact that patients with ATTRwt amyloidosis are increasingly diagnosed at an earlier stage of the disease.**10** In addition, the profile of patients diagnosed with ATTRwt amyloidosis is changing. For example, diagnoses of ATTRwt amyloidosis have increased in women and patients aged >80 years.**10**,**11** In addition, although the mean age at diagnosis has increased over time, diagnoses in younger patients have also been reported.**12** However, there is limited information about how the clinical manifestations of ATTRwt amyloidosis may differ according to age and sex. The objective of this analysis from the Transthyretin Amyloidosis Outcomes Survey (THAOS) was to compare baseline characteristics of patients with ATTRwt amyloidosis among 4 different age groups (<70 years, 70-79 years, 80-89 years, and ≥90 years) in the whole ATTRwt amyloidosis cohort and in male and female patients with ATTRwt amyloidosis.

Methods

Study design and population

THAOS was the largest global, longitudinal, observational study of patients with ATTR amyloidosis, including both ATTRv and ATTRwt amyloidosis, and asymptomatic carriers of pathogenic *TTR* gene variants, and was completed on June 16, 2023. The overall design and methodology of THAOS have been described in detail.**13** This analysis included all patients with ATTRwt amyloidosis enrolled in THAOS who had not received any disease-modifying treatment (data cutoff date: August 1, 2022).

All THAOS sites received ethical or Institutional Review Board approval before patient enrollment, and each patient provided written informed

consent. The study followed the Good Pharmacoepidemiology Practice guidelines and the principles of the Declaration of Helsinki.

Assessments

Assessments included those of general wellness (eg, modified body mass index [BMI] and Karnofsky Performance Status) and a range of cardiac parameters. Modified BMI was calculated by multiplying BMI by the serum albumin level to compensate for fluid accumulation. The Karnofsky Performance Status score is a measure of a patient's ability to perform normal daily life activities and their need for assistance; scores range from 10 (moribund; fatal processes progressing rapidly) to 100 (normal; no complaints). Cardiac parameters included NYHA functional class, presence of a pacemaker, electrocardiogram (ECG) and echocardiogram findings, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration. Carpal tunnel syndrome and other comorbidities were also assessed. Phenotype at enrollment is also reported based on previously published criteria.**14**

Statistical analysis

Patients were grouped by age at enrollment into 1 of 4 groups: <70 years, 70 to 79 years, 80 to 89 years, and ≥90 years. Demographic and clinical characteristics at enrollment were compared between age groups in the overall ATTRwt amyloidosis cohort and among male and female patients only. Nominal *P* values were from the chi-square test for categorical variables, 1-way analysis of variance for means of continuous variables, and the Wilcoxon test for medians of continuous variables.

Results

Demographic and general clinical characteristics

A total of 1,251 patients with ATTRwt amyloidosis from 53 centers in 15 countries were included in the analysis; 171 (13.7%) were aged <70 years, 614 (49.1%) were aged 70 to 79 years, 431 (34.5%) were aged 80 to 89 years,

and 35 (2.8%) were aged ≥90 years. Overall, the majority of patients were men (93.2%) (**Table 1**). The proportion of women increased with age from 4.1% in patients <70 years old to 14.3% in patients ≥90 years old. Median time from symptom onset to diagnosis was 1.8 years overall and did not differ between age groups (**Table 1**, **Central Illustration**). Median time from symptom onset to diagnosis was numerically highest in women aged <70 years at 5.2 years. Similarly, median time from first definitely related symptom to enrollment in THAOS did not differ between age groups and was numerically highest in women aged <70 years at 5.9 years (**Table 1**).

Table 1Demographic and General Clinical Characteristics According to Age at Enrollment and Sex	**Overall (N = 1,251)**	**Age <70 y (n = 171)**	**Age 70-79 y (n = 614)**	**Age 80-89 y (n = 431)**	**Age ≥90 y (n = 35)**	***P* Value a**
Sex						0.005
Male (n = 1,166)	1,166 (93.2)	164 (95.9)	582 (94.8)	390 (90.5)	30 (85.7)	-
Female (n = 85)	85 (6.8)	7 (4.1)	32 (5.2)	41 (9.5)	5 (14.3)	-
Age at enrollment (y)						
Overall (n = 1,251)	77.4 (68.5, 86.2)	66.3 (59.7, 69.5)	75.5 (71.4, 79.2)	83.7 (80.6, 87.7)	91.3 (90.2, 95.7)	-
Male (n = 1,166)	77.3 (68.5, 85.8)	66.3 (59.7, 69.5)	75.4 (71.4, 79.2)	83.7 (80.6, 87.6)	91.3 (90.3, 95.5)	-
Female (n = 85)	80.3 (70.6, 88.4)	68.2 (49.6, 69.4)	76.1 (71.8, 79.0)	83.9 (80.5, 88.3)	92.1 (90.1, 96.6)	-

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Age at symptom onset (y)						
Overall (n = 1,150)	72.8 (60.0, 82.7)	61.5 (52.5, 67.5)	71.5 (61.5, 77.0)	79.5 (70.4, 84.8)	89.8 (84.0, 93.5)	-
Male (n = 1,070)	72.6 (60.0, 82.5)	61.5 (52.5, 68.0)	71.5 (61.5, 77.0)	79.5 (70.5, 84.5)	90.0 (84.0, 93.5)	-
Female (n = 80)	75.3 (59.3, 85.7)	61.5 (42.5, 65.5)	71.9 (59.3, 75.7)	80.8 (61.5, 85.9)	87.5 (80.0, 95.5)	-
Time from symptom onset to diagnosis (y)						
Overall (n = 1,081)	1.8 (0.0, 12.2)	1.7 (0.0, 11.8)	2.0 (0.0, 13.3)	1.8 (0.0, 12.2)	0.7 (0.0, 5.7)	0.167
Male (n = 1,007)	1.8 (0.0, 12.2)	1.3 (0.0, 12.0)	2.0 (0.0, 13.3)	1.9 (0.0, 11.8)	0.6 (0.0, 4.0)	0.072
Female (n = 74)	1.6 (0.0, 16.6)	5.2 (0.1, 11.4)	2.2 (0.0, 16.6)	0.8 (0.0, 16.8)	2.5 (0.4, 11.8)	0.397
Time from first definitely related symptom to enrollment (y)						
Overall (n = 1,150)	2.9 (0.3, 13.2)	2.3 (0.2, 12.4)	3.0 (0.4, 13.7)	3.1 (0.4, 13.2)	1.9 (0.3, 6.8)	0.134

Table 1Demographic and General Clinical Characteristics According to Age at Enrollment and Sex	**Overall (N = 1,251)**	**Age <70 y (n = 171)**	**Age 70-79 y (n = 614)**	**Age 80-89 y (n = 431)**	**Age ≥90 y (n = 35)**	***P* Value[a]**
Male (n = 1,070)	3.0 (0.3, 13.2)	2.2 (0.1, 12.6)	3.1 (0.3, 13.7)	3.2 (0.4, 12.7)	1.8 (0.2, 6.8)	0.041
Female (n = 80)	2.5 (0.6, 16.8)	5.9 (1.8, 11.5)	2.6 (0.6, 15.0)	1.9 (0.5, 19.6)	5.4 (0.8, 12.1)	0.328
Follow-up time (y)						
Overall (n = 1,251)	2.3 (0.4, 5.3)	3.1 (0.5, 6.7)	2.5 (0.5, 5.6)	2.0 (0.4, 4.0)	1.4 (0.0, 2.4)	<0.001
Male (n = 1,166)	2.3 (0.4, 5.3)	3.0 (0.5, 6.7)	2.5 (0.5, 5.6)	2.0 (0.4, 4.1)	1.6 (0.0, 2.6)	<0.001
Female (n = 85)	1.6 (0.1, 5.5)	4.4 (0.0, 7.4)	2.2 (0.5, 6.3)	1.3 (0.2, 3.2)	0.9 (0.0, 1.4)	0.016
Phenotype						
Overall (n = 1,142)						0.081
Predominantly cardiac	901 (78.9)	115 (75.7)	450 (79.5)	316 (80.6)	20 (62.5)	
Mixed	241 (21.1)	37 (24.3)	116 (20.5)	76 (19.4)	12 (37.5)	
Male (n = 1,062)						0.271

Table 1Demographic and General Clinical Characteristics According to Age at Enrollment and Sex	**Overall (N = 1,251)**	**Age <70 y (n = 171)**	**Age 70-79 y (n = 614)**	**Age 80-89 y (n = 431)**	**Age ≥90 y (n = 35)**	***P* Value[a]**
Predominantly cardiac	843 (79.4)	111 (76.6)	428 (79.9)	286 (80.8)	18 (66.7)	
Mixed	219 (20.6)	34 (23.4)	108 (20.1)	68 (19.2)	9 (33.3)	
Female (n = 80)						0.204
Predominantly cardiac	58 (72.5)	4 (57.1)	22 (73.3)	30 (78.9)	2 (40.0)	
Mixed	22 (27.5)	3 (42.9)	8 (26.7)	8 (21.1)	3 (60.0)	
mBMI						
Overall (n = 764)	1,065.2 (820.9, 1,322.7)	1,113.5 (836.0, 1,404.9)	1,091.0 (831.0, 1,340.3)	1,026.5 (815.0, 1,263.2)	892.8 (763.9, 1,221.9)	<0.001
Male (n = 705)	1,066.8 (820.9, 1,322.3)	1,120.3 (829.0, 1,418.5)	1,092.0 (831.0, 1,339.9)	1,017.3 (813.9, 1,256.7)	880.7 (769.8, 1,174.2)	<0.001
Female (n = 59)	1,046.6 (816.2, 1,360.3)	999.6 (947.6, 1,076.6)	1,046.6 (856.8, 1,373.7)	1,054.8 (816.2, 1,335.1)	952.0 (711.8, 1,300.0)	0.756
Karnofsky Performance Status						
Overall (n = 515)						<0.001
80–100	338 (65.6)	58 (82.9)	174 (69.9)	96 (53.9)	10 (55.6)	

Table 1Demographic and General Clinical Characteristics According to Age at Enrollment and Sex	**Overall (N = 1,251)**	**Age <70 y (n = 171)**	**Age 70-79 y (n = 614)**	**Age 80-89 y (n = 431)**	**Age ≥90 y (n = 35)**	***P* Value a**
50–70	167 (32.4)	9 (12.9)	73 (29.3)	77 (43.3)	8 (44.4)	
10–40	10 (1.9)	3 (4.3)	2 (0.8)	5 (2.8)	0 (0.0)	
Male (n = 468)						0.008
80–100	311 (66.5)	53 (81.5)	162 (69.8)	87 (55.4)	9 (64.3)	
50–70	148 (31.6)	9 (13.8)	68 (29.3)	66 (42.0)	5 (35.7)	
10–40	9 (1.9)	3 (4.6)	2 (0.9)	4 (2.5)	0 (0.0)	
Female (n = 47)						0.080
80–100	27 (57.4)	5 (100.0)	12 (70.6)	9 (42.9)	1 (25.0)	
50–70	19 (40.4)	0 (0.0)	5 (29.4)	11 (52.4)	3 (75.0)	
10–40	1 (2.1)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	
Bilateral carpal tunnel syndrome						
Overall (n = 1,251)	218 (17.4)	35 (20.5)	110 (17.9)	67 (15.5)	6 (17.1)	0.507
Male (n = 1,166)	198 (17.0)	32 (19.5)	103 (17.7)	58 (14.9)	5 (16.7)	0.508
Female (n = 85)	20 (23.5)	3 (42.9)	7 (21.9)	9 (22.0)	1 (20.0)	0.647
Kidney involvement						

Table 1Demographic and General Clinical Characteristics According to Age at Enrollment and Sex	**Overall (N = 1,251)**	**Age <70 y (n = 171)**	**Age 70-79 y (n = 614)**	**Age 80-89 y (n = 431)**	**Age ≥90 y (n = 35)**	***P* Value a**
Overall (n = 1,251)	12 (1.0)	2 (1.2)	6 (1.0)	4 (0.9)	0	0.890
Male (n = 1,166)	10 (0.9)	2 (1.2)	4 (0.7)	4 (1.0)	0	0.799
Female (n = 85)	2 (2.4)	0	2 (6.3)	0	0	0.403
Vitreal involvement						
Overall (n = 1,251)	16 (1.3)	2 (1.2)	6 (1.0)	8 (1.9)	0	0.640
Male (n = 1,166)	16 (1.4)	2 (1.2)	6 (1.0)	8 (2.1)	0	0.597
Female (n = 85)	0	0	0	0	0	-
Diabetes mellitus						
Overall (n = 1,251)	164 (13.1)	22 (12.9)	68 (11.1)	66 (15.3)	8 (22.9)	0.071
Male (n = 1,166)	148 (12.7)	21 (12.8)	62 (10.7)	59 (15.1)	6 (20.0)	0.107
Female (n = 85)	16 (18.8)	1 (14.3)	6 (18.8)	7 (17.1)	2 (40.0)	0.601
Inflammatory arthritis						
Overall (n = 1,251)	60 (4.8)	6 (3.5)	33 (5.4)	18 (4.2)	3 (8.6)	0.420
Male (n = 1,166)	56 (4.8)	4 (2.4)	33 (5.7)	17 (4.4)	2 (6.7)	0.277
Female (n = 85)	4 (4.7)	2 (28.6)	0	1 (2.4)	1 (20.0)	0.009
Osteoarthritis						
Overall (n =	179	22	88	62	7 (20.0)	0.717

Table 1Demographic and General Clinical Characteristics According to Age at Enrollment and Sex	**Overall (N = 1,251)**	**Age <70 y (n = 171)**	**Age 70-79 y (n = 614)**	**Age 80-89 y (n = 431)**	**Age ≥90 y (n = 35)**	***P* Value[a]**
1,251)	(14.3)	(12.9)	(14.3)	(14.4)		
Male (n = 1,166)	170 (14.6)	21 (12.8)	85 (14.6)	58 (14.9)	6 (20.0)	0.732
Female (n = 85)	9 (10.6)	1 (14.3)	3 (9.4)	4 (9.8)	1 (20.0)	0.618

Values are n (%) or median (10th, 90th percentile). Available n (male, female) for variables with missing data in the respective age groups: age at symptom onset: 156 (149, 7), 571 (541, 30), 391 (353, 38), and 32 (27, 5); time from symptom onset to diagnosis: 145 (138, 7), 541 (513, 28), 367 (332, 35), and 28 (24, 4); mBMI: 101 (97, 4), 387 (364, 23), 250 (221, 29), 26 (23, 3); phenotype: 152 (145, 7), 566 (536, 30), 392 (354, 38), 32 (27, 5); Karnofsky Performance Status score: 70 (65, 5), 249 (232, 17), 178 (157, 21), 18 (14, 4). ATTRwt amyloidosis = wild-type transthyretin amyloidosis; mBMI = modified body mass index.

a *P* values are nominal and not indicative of statistical significance.

Age and Sex Differences in Patients With ATTRwt Amyloidosis

A total of 1,251 patients with ATTRwt amyloidosis from the Transthyretin Amyloidosis Outcomes Survey were included in this analysis; most were aged 70 to 79 or 80 to 89 years and male. Median time from symptom onset to diagnosis was ~ 2 years overall and was numerically highest in women aged <70 years. The proportion of patients with NYHA functional class III/IV heart failure and Karnofsky Performance Status (KPS) scores ≤70 generally increased with age, indicating greater disease severity. ATTRwt amyloidosis = wild-type transthyretin amyloidosis.

A majority of patients had a predominantly cardiac phenotype (78.9%) with the rest having a mixed phenotype (21.1%) (**Table 1**). Phenotype distribution did not differ between age groups or between men and women.

Modified BMI and Karnofsky Performance Status score differed by age. Median modified BMI decreased with age from 1,113.5 in patients aged <70 years to 892.8 in patients aged ≥90 years (**Table 1**). The same pattern was observed in men, but there was no clear age-related pattern in women. The proportion with a Karnofsky Performance Status score ≤70, indicating the patient is unable to work and requires assistance for self-care, generally increased with age from 17.1% in patients aged <70 years to 44.4% in patients aged ≥90 (**Table 1**, **Central Illustration**).

The incidence of comorbidities was generally similar across age groups (**Table 1**). The incidence of bilateral carpal tunnel syndrome was 17.4% and was numerically higher in women than men in all age groups. Median time from bilateral carpal tunnel syndrome onset to cardiomyopathy onset was 8.9 years in all patients, 8.4 years in men, and 9.2 years in women.

Cardiac parameters

ECG abnormalities were observed in most patients, but the proportion of patients with ECG abnormalities increased with age in the overall population (**Table 2**). Mean NT-proBNP concentration generally increased with age, as did the proportion with NYHA functional class III/IV heart failure, reflecting more advanced disease in older patients (**Table 2**, **Figure 1**, **Central Illustration**). The same pattern in NT-proBNP concentration and NYHA functional class was observed among men, but no clear age-related pattern was observed among women.

Table 2Cardiac Characteristics of Patients With ATTRwt Amyloidosis According to Age at Diagnosis and Sex	**Overall (N = 1,251)**	**Age <70 y (n = 171)**	**Age 70-79 y (n = 614)**	**Age 80-89 y (n = 431)**	**Age ≥90 y (n = 35)**	***P* Value a**
Abnormal ECG						
Overall (n = 1,074)	1,003/1,074 (93.4)	136/154 (88.3)	491/527 (93.2)	350/367 (95.4)	26/26 (100.0)	0.014
Male (n = 999)	936/999 (93.7)	130/147 (88.4)	466/499 (93.4)	318/331 (96.1)	22/22 (100.0)	0.009
Female (n = 75)	67/75 (89.3)	6/7 (85.7)	25/28 (89.3)	32/36 (88.9)	4/4 (100.0)	0.901
Complete AV block or pacemaker						
Overall (n = 953)	405/953 (42.5)	52/133 (39.1)	201/473 (42.5)	143/322 (44.4)	9/25 (36.0)	0.672
Male (n = 889)	386/889 (43.4)	50/127 (39.4)	195/448 (43.5)	133/293 (45.4)	8/21 (38.1)	0.669
Female (n = 64)	19/64 (29.7)	2/6 (33.3)	6/25 (24.0)	10/29 (34.5)	1/4 (25.0)	0.853
LAHB						
Overall (n = 669)	160/669 (23.9)	21/97 (21.6)	75/344 (21.8)	57/210 (27.1)	7/18 (38.9)	0.209
Male (n = 626)	143/626 (22.8)	18/92 (19.6)	70/326 (21.5)	50/193 (25.9)	5/15 (33.3)	0.412
Female (n = 43)	17/43 (39.5)	3/5 (60.0)	5/18 (27.8)	7/17 (41.2)	2/3 (66.7)	0.414
LPHB						

Table 2Cardiac Characteristics of Patients With ATTRwt Amyloidosis According to Age at Diagnosis and Sex	**Overall (N = 1,251)**	**Age <70 y (n = 171)**	**Age 70-79 y (n = 614)**	**Age 80-89 y (n = 431)**	**Age ≥90 y (n = 35)**	***P* Value[a]**
Overall (n = 669)	13/669 (1.9)	3/97 (3.1)	8/344 (2.3)	2/210 (1.0)	0/18 (0.0)	0.515
Male (n = 626)	13/626 (2.1)	3/92 (3.3)	8/326 (2.5)	2/193 (1.0)	0/15 (0.0)	0.554
Female (n = 43)	0/43 (0.0)	0/5 (0.0)	0/18 (0.0)	0/17 (0.0)	0/3 (0.0)	-
LBBB						
Overall (n = 670)	93/670 (13.9)	8/97 (8.2)	45/344 (13.1)	35/211 (16.6)	5/18 (27.8)	0.073
Male (n = 627)	85/627 (13.6)	8/92 (8.7)	41/326 (12.6)	32/194 (16.5)	4/15 (26.7)	0.124
Female (n = 43)	8/43 (18.6)	0/5 (0.0)	4/18 (22.2)	3/17 (17.6)	1/3 (33.3)	0.757
RBBB						
Overall (n = 673)	172/673 (25.6)	22/97 (22.7)	95/345 (27.5)	52/213 (24.4)	3/18 (16.7)	0.567
Male (n = 630)	158/630 (25.1)	20/92 (21.7)	88/327 (26.9)	48/196 (24.5)	2/15 (13.3)	0.519
Female (n = 43)	14/43 (32.6)	2/5 (40.0)	7/18 (38.9)	4/17 (23.5)	1/3 (33.3)	0.780
Pacemaker						
Overall (n = 1,251)	177 (14.1)	17 (9.9)	73 (11.9)	84 (19.5)	3 (8.6)	0.001

Table 2Cardiac Characteristics of Patients With ATTRwt Amyloidosis According to Age at Diagnosis and Sex	**Overall (N = 1,251)**	**Age <70 y (n = 171)**	**Age 70-79 y (n = 614)**	**Age 80-89 y (n = 431)**	**Age ≥90 y (n = 35)**	***P* Value a**
Male (n = 1,166)	170 (14.6)	17 (10.4)	71 (12.2)	79 (20.3)	3 (10.0)	0.001
Female (n = 85)	7 (8.2)	0 (0.0)	2 (6.3)	5 (12.2)	0 (0.0)	0.820
NT-proBNP (pg/mL)						
Overall (n = 805)	4,429.6 ± 7,543.2	3,716.1 ± 9,433.0	3,621.0 ± 4,946.5	5,778.5 ± 9,110.9	6,891.6 ± 12,772.8	<0.001
Male (n = 752)	4,303.8 ± 7,373.0	3,630.3 ± 9,519.7	3,428.4 ± 4,350.9	5,729.9 ± 9,078.2	7,467.5 ± 13,418.9	<0.001
Female (n = 53)	6,213.4 ± 9,549.2	5,216.2 ± 8,350.8	6,694.9 ± 10,345.3	6,349.7 ± 9,700.7	1,997.0 ± 1,405.7	0.919
Diastolic interventricular septum wall thickness (mm)						
Overall (n = 919)	17.4 ± 3.6	17.1 ± 3.7	17.5 ± 3.7	17.3 ± 3.5	17.2 ± 3.4	0.650
Male (n = 865)	17.4 ± 3.6	17.3 ± 3.6	17.6 ± 3.7	17.3 ± 3.5	16.1 ± 2.4	0.348
Female (n = 54)	16.9 ± 3.9	14.2 ± 4.5	16.8 ± 3.6	17.0 ± 3.3	21.7 ± 3.5	0.019
Diastolic interventricular septum wall thickness (mm)/height (m)						
Overall (n =	10.1 ± 2.3	9.9 ± 2.6	10.1 ±	10.1 ±	10.4 ±	0.698

Table 2Cardiac Characteristics of Patients With ATTRwt Amyloidosis According to Age at Diagnosis and Sex	**Overall (N = 1,251)**	**Age <70 y (n = 171)**	**Age 70-79 y (n = 614)**	**Age 80-89 y (n = 431)**	**Age ≥90 y (n = 35)**	***P* Value a**
905)			2.2	2.4	2.5	
Male (n = 851)	10.0 ± 2.3	10.0 ± 2.6	10.0 ± 2.2	10.1 ± 2.5	9.5 ± 1.5	0.713
Female (n = 54)	10.6 ± 2.5	8.6 ± 2.7	10.5 ± 2.4	10.6 ± 2.1	14.1 ± 2.2	0.004
LV mean wall thickness (mm)						
Overall (n = 936)	16.4 ± 3.1	16.4 ± 3.2	16.5 ± 3.1	16.2 ± 2.9	16.2 ± 3.2	0.618
Male (n = 881)	16.4 ± 3.0	16.5 ± 3.1	16.6 ± 3.1	16.2 ± 2.9	15.2 ± 2.4	0.180
Female (n = 55)	15.8 ± 3.2	14.4 ± 4.1	15.4 ± 3.2	15.9 ± 2.5	20.5 ± 2.1	0.013
LV mean wall thickness (mm)/height (m)						
Overall (n = 922)	9.5 ± 2.0	9.4 ± 2.4	9.5 ± 1.9	9.5 ± 2.1	9.8 ± 2.3	0.906
Male (n = 867)	9.5 ± 2.0	9.5 ± 2.3	9.5 ± 1.8	9.5 ± 2.1	8.9 ± 1.5	0.725
Female (n = 55)	9.9 ± 2.2	8.7 ± 2.5	9.6 ± 2.2	9.9 ± 1.7	13.3 ± 1.4	0.003
LVEF (%)						
Overall (n = 927)	48.4 ± 12.5	49.3 ± 13.7	48.6 ± 12.2	47.5 ± 12.4	51.4 ± 14.1	0.309

Table 2Cardiac Characteristics of Patients With ATTRwt Amyloidosis According to Age at Diagnosis and Sex	**Overall (N = 1,251)**	**Age <70 y (n = 171)**	**Age 70-79 y (n = 614)**	**Age 80-89 y (n = 431)**	**Age ≥90 y (n = 35)**	***P* Value[a]**
Male (n = 874)	48.2 ± 12.4	49.2 ± 13.4	48.4 ± 12.1	47.1 ± 12.2	50.4 ± 14.2	0.309
Female (n = 53)	52.2 ± 14.3	53.0 ± 19.3	50.7 ± 13.7	53.1 ± 13.9	55.3 ± 15.3	0.919

Values are n/N (%), n (%), or mean ± SD. Available n (male, female) for variables with missing data in the respective age groups: NT-proBNP: 111 (105, 6), 407 (383, 24), 268 (247, 21), 19 (17, 2); diastolic interventricular septum wall thickness: 136 (129, 7), 455 (433, 22), 308 (287, 21), and 20 (16, 4); diastolic interventricular septum wall thickness/height: 134 (127, 7), 448 (426, 22), 303 (282, 21), 20 (16, 4); LV wall thickness: 144 (137, 7), 458 (435, 23), 314 (293, 21), and 20 (16, 4); LV mean wall thickness/height: 142 (135, 7), 451 (428, 23), 309 (288, 21), and 20 (16, 4); LVEF: 144 (137, 7), 453 (430, 23), 310 (291, 19), and 20 (16,4).

ATTRwt amyloidosis = wild-type transthyretin amyloidosis; AV = atrioventricular; ECG = electrocardiogram; LAHB = left anterior hemiblock; LBBB = left bundle branch block; LPHB = left posterior hemiblock; LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RBBB = right bundle branch block.

Left ventricular (LV) wall thickness and other structural and functional cardiac measures did not differ between age groups (**Table 2**). Men versus women had numerically higher diastolic interventricular septum wall thickness and LV mean wall thickness, but these measures were numerically higher in women when indexed by height. Diastolic

interventricular septum wall thickness and LV mean wall thickness increased with age in women but stayed relatively stable across age groups in men. Mean LV ejection fraction was numerically higher in women than men in all age groups, but there was no clear age-related pattern.

Discussion

ATTRwt amyloidosis is a condition that is primarily diagnosed in elderly men, although recent reports have revealed an increase in diagnoses in women and younger patients. This analysis from the THAOS database examined age- and sex-related differences in baseline characteristics in more than 1,200 patients with ATTRwt amyloidosis.

In this analysis, 13.7% of patients with ATTRwt amyloidosis were aged <70 years at enrollment. Although this cohort tended to present with less severe disease than older patients, a considerable proportion exhibited significant functional impairment and advanced cardiac disease. Specifically, 17.1% of patients with ATTRwt amyloidosis aged <70 years had a Karnofsky score at or below 70, indicating that they were unable to work and required varying levels of assistance with everyday activities or frequent medical care. Furthermore, 23.3% of patients had NYHA functional class III or IV heart failure at enrollment, suggesting that ATTRwt amyloidosis is often diagnosed late in the disease course in this age group. The proportion of patients with ECG abnormalities also increased with age, but this is not unexpected given the age of these patients and could be related to conditions other than ATTRwt amyloidosis.

Median time from symptom onset to diagnosis was ~ 2 years in this group of patients. One factor that may contribute to the delay in diagnosis is that many patients in THAOS were diagnosed using biopsy, before the advent of scintigraphy, and biopsy has been linked with delayed diagnosis of ATTR amyloidosis. One of the most striking findings was that the median time from symptom onset to diagnosis was longest among women aged <70 years at 5 years. This may be a consequence of the historical association of

ATTRwt amyloidosis with elderly men, resulting in lower clinical suspicion and delayed diagnosis in women aged <70 years, and highlights an important area of improvement in patient screening. Delayed diagnosis in patients with ATTRwt amyloidosis has been previously reported,**15** and the current study suggests that women aged <70 years may be the most impacted.

Recent reports indicate that women may make up a greater proportion of ATTRwt amyloidosis patients than previously thought, with some studies reporting rates as high as 20%.**4**,**16** Although men accounted for over 90% of patients in the current analysis, consistent with a prior THAOS analysis of patients with ATTRwt amyloidosis,**17** the proportion of women increased with age. The prior THAOS analysis and other studies have suggested that women with ATTRwt amyloidosis have a later age at onset and milder cardiac phenotype than men.**4**,**17**,**18** In line with these prior findings, women in this cohort were, on average, older at symptom onset and at enrollment. Diastolic interventricular septum and LV mean wall thickness were numerically lower in women than men, although women had slightly higher measures when indexed by height. It has been suggested that a uniform LV wall thickness threshold to screen for transthyretin amyloid cardiomyopathy in men and women could lead to underdiagnosis in women**19** and that an indexed threshold should be used instead.**20** Our finding of greater wall thickness in women when indexed by height supports this position. We also observed that diastolic interventricular septum thickness and LV mean wall thickness increased with age in women but not in men, and women aged ≥90 years had numerically higher measures than men in the same age group. Despite this, mean NT-proBNP concentration was lower and LV ejection fraction higher in women than men aged ≥90 years, indicating less severe heart failure.

Study limitations

Our study has several limitations. The number of women in this analysis was small, with only 7 patients in the youngest cohort and 5 in the oldest,

thereby limiting our ability to draw robust conclusions from these data. Findings should be confirmed in larger samples. Prognostic data were not available for this analysis, so we were not able to assess whether cardiac manifestations were associated with worse outcomes. The THAOS registry includes detailed data on cardiac manifestations, but fewer details were available for neuropathy and musculoskeletal symptoms in ATTRwt amyloidosis. This may be the result of underreporting due to inconsistent assessment across centers and the fact that these patients were seen or referred primarily by cardiologists who did not perform neurologic assessments. Additionally, given the small sample sizes for some of the cohorts, we were not able to examine how patient characteristics based on age and sex may have changed over the life of THAOS; future studies should look at temporal trends in these age- and sex-based findings. Lastly, some patients were missing cardiac and other baseline clinical data.

Conclusions

In this THAOS analysis, patients aged <70 years with ATTRwt amyloidosis had less severe disease than older patients. Nevertheless, a substantial proportion displayed functional impairment and advanced heart failure. Importantly, women aged <70 years had the greatest diagnostic delay of all the cohorts at 5 years, which may be the result of low clinical suspicion in this patient population. The proportion of women with ATTRwt amyloidosis increased with age. Overall, this analysis provides important information about the clinical manifestations of ATTRwt amyloidosis across different age groups and in men and women.

7. Women Undergoing CABG More Likely to Get Care at Low-Quality Hospitals

Female Medicare beneficiaries undergoing coronary artery bypass grafting are more likely to receive care at low-quality hospitals than male

beneficiaries, with a greater sex disparity in mortality at low-quality hospitals, according to a study published online June 11 in JAMA Network Open.

Catherine M. Wagner, M.D., and Andrew M. Ibrahim, M.D., from the University of Michigan in Ann Arbor, examined sex disparities in 30-day mortality after coronary artery bypass grafting across high- and low-quality hospitals in a cross-sectional, retrospective cohort study. A total of 444,855 beneficiaries were analyzed (27.1 and 72.9 percent female and male, respectively).

The researchers found that female beneficiaries were more likely to have an unplanned admission than male beneficiaries, and they were more likely to receive care at low- versus high-quality hospitals (odds ratio, 1.26). Risk-adjusted female and male mortality was 4.24 and 2.75 percent, respectively, overall, with an absolute difference of 1.48 percentage points. Male and female mortality was 1.57 and 2.58 percent at the highest-quality hospitals, compared with 4.94 and 7.02 percent at the lowest-quality hospitals (absolute differences, 1.01 and 2.07 percentage points, respectively). More than fourfold higher mortality was seen for female beneficiaries receiving care at low-quality hospitals than male beneficiaries who received care at high-quality hospitals (7.02 versus 1.57 percent).

"Policy aimed at equitable referral of female patients to high-quality centers and targeted improvement of low-quality hospitals may narrow these disparities," the authors write.

8. Sex, Race, and Rural-Urban Disparities in VT Ablations

Study Questions:

Are there differences in patients hospitalized with ventricular tachycardia (VT) who received catheter ablations with potential disparities in access and utilization of VT ablation?

Methods:

The investigators used the National Inpatient Sample to assess patients hospitalized with a primary diagnosis of VT in 2019 who did and did not receive catheter ablations. Multiple logistic regression was used to calculate risk factors for VT ablation based on age, sex, race/ethnicity, socioeconomic status, and hospital characteristics.

Results:

After adjusting for baseline characteristics and comorbidities, female and Black patients hospitalized with VT had significantly lower odds of receiving ablations compared to male and White patients (odds ratio [OR], 0.835; 95% confidence interval [CI], 0.699-0.997; p = 0.047 and OR, 0.617; 95% CI, 0.457-0.832; p = 0.002), respectively. Additionally, patients at rural or nonteaching hospitals were significantly less likely to receive ablations compared to those at urban teaching hospitals. No significant differences were noted based on income or insurance status in the adjusted models.

Conclusions:

The authors report significant disparities in the delivery of ventricular ablations among patients hospitalized with VT.

Perspective:

This study reports significant disparities among patients with VT undergoing ablation in the inpatient setting, even after adjusting for baseline demographics and comorbidities. Of note, female patients were roughly 15% less likely to receive ablations compared to males and Black patients were nearly 40% less likely to receive ablations compared to White patients. Furthermore, patients admitted to rural and nonteaching hospitals were 60-85% less likely to undergo ablation compared to those at urban teaching hospitals. These findings suggest that VT ablation may be underutilized in historically marginalized patient populations and that a large urban-rural divide in access to care may exist. Additional studies are indicated to better

understand mechanisms underlying disparities in VT ablation and to assess interventions likely to be effective in mitigating these disparities.

9. Improving CV Health in Pregnancy May Decrease Risk for Depression Postpartum

A third of women develop gestational hypertension, gestational diabetes, preeclampsia, or eclampsia during pregnancy. These pregnancy complications are associated with risk for postpartum psychological distress and future cardiovascular disease (CVD).

This study was a secondary analysis of data collected for a longitudinal study that calculated a CVH score on the basis of the American Heart Association (AHA) Life's Essential 8 (LE8). Women (N=257) who were overweight or obese prior to pregnancy were recruited at 12 to 20 weeks' gestation. At baseline and 6 months postpartum, CVH scores were evaluated and related with postpartum psychological distress, assessed using the Center for Epidemiologic Studies-Depression Scale (CES-D) and Perceived Stress Scale (PSS) instruments. The LE8 comprised diet quality, physical activity, nicotine use, sleep duration, BMI, blood pressure, blood lipids, and blood glucose components but the CVH score did not include blood metrics.

At baseline, the women had a mean age of 28.43 (SD, 5.40) years, they were mean 15.64 (SD, 2.45) weeks pregnant, they had a mean prepregnancy BMI of 32.7 (SD, 6.55), a mean CES-D score of 12.46 (SD, 9.88), a mean PSS score of 20.91 (SD, 8.73), and a mean CVH score of 53.05 (SD, 15.03).

…worsening of CVH behaviors from pregnancy to postpartum is longitudinally associated with more severe depressive symptoms and greater perceived stress at 6 months postpartum among individuals at high risk for future CVD.

At 6 months postpartum, CES-D scores decreased to a mean of 10.75 (SD, 9.58), mean PSS scores were similar at 20.73 (SD, 8.97), and mean CVH scores decreased to 41.97 (SD, 19.98). Overall, 22.6% of women were at risk for a depressive episode.

From baseline to 6 months postpartum, CVH scores for BMI (t[225], 2.92; P <.01), sleep (t[112], 5.69; P <.01), and physical activity (t[225], -3.91; P <.01) changed significantly whereas no changes were observed for dietary intake or nicotine use.

Excluding the sleep outcome, worsening CVH scores associated with risk for postpartum depressive episode (b, -0.18; P <.01) and worse perceived stress (b, -0.13; P =.02). Individuals whose CVH worsened by more than 1 standard deviation had more severe CES-D (mean, 3.53 vs 2.59) and PSS (mean, 23.34 vs 17.88) scores compared with those who had improvement by more than one SD.

Improved CVH scores were associated with decreased risk for a depressive episode postpartum (odds ratio [OR], 0.975; 95% CI, -0.049 to -0.002; P =.04).

When sleep was included in the CVH score, the change in CVH scores from pregnancy to postpartum did not associate with CES-D (b, 0.06; P =.4) or PSS (b, 0.04; P =.6) outcomes. However, sleep at 6 months postpartum correlated with current depressive symptoms (r, 0.40; P <.01) and perceived stress (r, 0.31; P <.01).

This study was limited by the fact that sleep was incorporated into the CVH score halfway through the study, so only 50.4% of women had data about sleep at baseline.

The study authors concluded, "…worsening of CVH behaviors from pregnancy to postpartum is longitudinally associated with more severe depressive symptoms and greater perceived stress at 6 months postpartum among individuals at high risk for future CVD."

10. Relationship of Sex and Body Size With Cardiac Resynchronization Therapy Benefit

BACKGROUND

Women might benefit more than men from cardiac resynchronization therapy (CRT) and do so at shorter QRS durations.

OBJECTIVE

This meta-analysis was performed to determine whether sex-based differences in CRT effects are better accounted for by height, body surface area (BSA), or left ventricular end-diastolic dimension (LVEDD).

METHODS

We analyzed patient-level data from CRT trials (MIRACLE, MIRACLE ICD, MIRACLE ICD II, REVERSE, RAFT, COMPANION, and MADIT-CRT) using bayesian hierarchical Weibull regression models. Relationships between QRS duration and CRT effects were examined overall and in sex-stratified cohorts; additional analyses indexed QRS duration by height, BSA, or LVEDD. End points were heart failure hospitalization (HFH) or death and all-cause mortality.

RESULTS

Compared with men (n = 5628), women (n = 1439) were shorter (1.62 [interquartile range, 1.57-1.65] m vs 1.75 [1.70-1.80] m; P < .001), with smaller BSAs (1.76 [1.62-1.90] m2 vs 2.02 [1.89-2.16] m2; P < .001). In adjusted sex-stratified analyses, the reduction in HFH or death was greater for women (hazard ratio, 0.54; credible interval, 0.42-0.70) than for men (hazard ratio, 0.77; credible interval, 0.66-0.89; Pinteraction = .009); results were similar for all-cause mortality even after adjustment for height, BSA, and LVEDD. Sex-specific differences were observed only in nonischemic cardiomyopathy. The effect of CRT on HFH or death was observed at a shorter QRS duration for women (126 ms) than for men (145 ms). Indexing QRS duration by height, BSA, or LVEDD attenuated sex-specific QRS duration thresholds for the effects of CRT on HFH or death but not on mortality.

CONCLUSION

Although body size partially explains sex-specific QRS duration thresholds for CRT benefit, it is not associated with the magnitude of CRT benefit.

Indexing QRS duration for body size might improve selection of patients for CRT, particularly with a "borderline" QRS duration.

11. Antihypertensive Medication Use in First 2 Years Postpartum

Study Questions:

What is the incidence of initiation of antihypertensive medication use in the first 2 years after delivery among women with hypertensive disorders of pregnancy (HDP)?

Methods:

This was a cohort study from a Danish registry of women with ≥1 pregnancy (≥20 weeks' gestation) who delivered from 1995 to 2018, with analysis conducted from 2022 to 2023. The National Prescription Registry was used to determine postpartum prescriptions of antihypertensive medications. The cumulative incidence and hazard ratios of initiating antihypertensive medication use was analyzed according to HDP status and antenatal medication use.

Results:

Of 784,782 women, 36,900 (4.7%) had an HDP versus no HDP (median age at delivery in both groups was 29 years). Women without an HDP had a 1.8% 2-year cumulative incidence of starting antihypertensive medications after delivery. Women with severe preeclampsia requiring antepartum medication had a 44.1% incidence of requiring antihypertensive medications at 2-years postpartum. Women who required postpartum antihypertensive medication most commonly started within 3 months of delivery; however, 13.4% (95% confidence interval [CI], 11.9%-14.1%) of women with severe preeclampsia, 24.7.% (95% CI, 24.0%-26.0%) of women with preeclampsia, 24.9% (95% CI, 22.5%-27.5%) of women with gestational hypertension, and 76.7% (95% CI, 76.3%-77.1%) of those without an HDP first filled a prescription for antihypertensive medication >3 months after delivery. Of women needing antihypertensive medication within the first 3 months

postpartum, up to 56% required further prescriptions >3 months postpartum.

Conclusions:

In this cohort study, the authors conclude that up to 44% of women with a pregnancy complicated by hypertensive disorders initiated use of antihypertensive medications within 2 years of delivery.

Perspective:

Prior studies have demonstrated the association of HDP with future risk of chronic hypertension; however, less is known about the timing of initiation of antihypertensive medications after delivery. This study shows a high percentage of patients with HDP required treatment for ongoing hypertension within the first 2 years after delivery. A portion of patients did not have a prescription filled within the first 3 months of delivery, but subsequently received antihypertensives within 2 years. This indicates that close postpartum follow-up is essential for reducing the risk of untreated hypertension. Ongoing efforts to better understand the systems of care for postpartum patients can help avoid delays in addressing postpartum hypertension.

12. Race and Sex Differences in Bystander CPR for Cardiac Arrest

Study Questions:

Is there a differential association between bystander cardiopulmonary resuscitation (CPR) and survival by sex and race and ethnicity of the patient with out-of-hospital cardiac arrest (OHCA)?

Methods:

The investigators identified 623,342 nontraumatic OHCAs during 2013 to 2022 within a large US registry for this observational cohort study. Using hierarchical logistic regression, the authors examined whether there was a

differential association between bystander CPR and survival outcomes by patients' sex and race and ethnicity, overall and by neighborhood strata.

Results:

The mean age was 62.1 ± 17.1 years, and 35.9% were women. Nearly half of patients (49.8%) were non-Hispanic White; 20.6% were non-Hispanic Black; 7.3% were Hispanic; 2.9% were Asian; and 0.4% were Native American. Overall, 58,098 (9.3%) survived to hospital discharge. Although bystander CPR was associated with higher survival in each race and ethnicity group, the association of bystander CPR compared with patients without bystander CPR in each racial and ethnic group was highest in individuals who were White (adjusted odds ratio [aOR], 1.33; 95% confidence interval [CI], 1.30-1.37) and Native American (aOR, 1.40; 95% CI, 1.02-1.90) and lowest in individuals who were Black (aOR, 1.09; 95% CI, 1.04-1.14; p for interaction < 0.001). The adjusted OR for bystander CPR compared with those without bystander CPR for Hispanic patients was 1.29 (95% CI, 1.20-1.139), for Asian patients, it was 1.27 (95% CI, 1.12-1.42), and for those of unknown race, it was 1.31 (95% CI, 1.25-1.36). Similarly, bystander CPR was associated with higher survival in both sexes, but its association with survival was higher in men (aOR, 1.35; 95% CI, 1.31-1.38) than women (aOR, 1.15; 95% CI, 1.12-1.19; p for interaction < 0.001). The weaker association of bystander CPR in Black individuals and women was consistent across neighborhood race and ethnicity and income strata. Similar results were observed for the outcome of survival without severe neurological deficits.

Conclusions:

The authors report that although bystander CPR was associated with higher survival in all patients, its association with survival was weakest for Black individuals and women with OHCA.

Perspective:

This registry study reports that association between bystander CPR and survival was weaker for Black individuals and women with OHCA compared with White individuals and men. Furthermore, these differential associations between bystander CPR and survival were observed across neighborhood race and ethnicity and income strata. These data suggest that efforts to reduce survival disparities for OHCA may require not only increasing CPR training rates in undertreated communities but also ensuring that bystander CPR, when initiated, is delivered with comparable effectiveness in all individuals with OHCA. Finally, additional studies are indicated to address disparities in bystander CPR care to ensure health care equity.

13. Early Pregnancy HbA1c As First Screening Test for Gestational Diabetes

BACKGROUND

More than 90% of gestational diabetes cases are estimated to occur in low-income and middle-income countries (LMICs). Most current guidelines recommend an oral glucose tolerance test (OGTT) at 24–28 weeks of gestation. The OGTT is burdensome, especially in LMICs, resulting in a high proportion of women not being screened. We aimed to develop a simple and effective screening strategy for gestational diabetes.

METHODS

STRiDE, a prospective cohort study, was set up in seven centres in south India and seven centres in western Kenya, and included pregnant women aged 18–50 years of age and at less than 16 weeks of gestation (<20 weeks in Kenya), confirmed by dating ultrasound. We assessed the efficacy of early pregnancy HbA1c (venous and capillary point-of-care), either alone or as part of a composite risk score with age, BMI, and family history of diabetes, in predicting gestational diabetes at 24–28 weeks of gestation, in two LMICs (India and Kenya) and in a UK multi-ethnic population from the PRiDE study. A key secondary outcome was to assess whether an early pregnancy composite risk score can reduce the need for OGTTs. Gestational diabetes was diagnosed using current WHO criteria.

FINDINGS

Between Feb 15, 2016, Dec 13, 2019, we enrolled 3070 participants in India and 4104 in Kenya. 4320 participants were included from the PRiDE cohort. Gestational diabetes prevalence by OGTT at 24–28 weeks was 19·2% in India, 3·0% in Kenya, and 14·5% in the UK. Early pregnancy HbA1c was independently associated with incidence of gestational diabetes at 24–28 weeks of gestation. Adjusted risk ratios were 1·60 (95% CI 1·19–2·16) in India, 3·49 (2·8–4·34) in Kenya, and 4·72 (3·82–5·82) in the UK. Composite risk score models that combined venous or point-of-care HbA1c with age, BMI, and family history of diabetes best predicted testing positive for gestational diabetes. A population-specific, two-threshold screening strategy of rule-in and rule-out gestational diabetes using early pregnancy composite risk score could reduce the requirement of OGTTs by 50–64%. For the HbA1c-alone model, the thresholds were 5·4% (rule in) and 4·9% (rule out) in India, 6·0% (rule in) and 5·2% (rule out) in Kenya, and 5·6% (rule in) and 5·2% (rule out) in the UK.

INTERPRETATION

Early pregnancy HbA1c offers a simple screening test for gestational diabetes, allowing those at highest risk to receive early intervention and greatly reduce the need for OGTTs. This can also be carried out using point-of-care HbA1c in LMICs.

14. IBD Increases Cardiovascular Complications Risk in Pregnant Patients During Delivery

BACKGROUND

Chronic inflammation in patients with IBD is associated with an increased risk for cardiovascular disease (CVD), the leading cause of maternal mortality, highlighting the need to investigate the effect of IBD on cardiovascular complications during pregnancy.

Therefore, researchers conducted an observational retrospective cohort study aimed to examine cardiovascular complications during childbirth in pregnant patients with IBD and identify the associated risk factors. The primary outcomes included cardiovascular complications (hypertensive disorders, myocardial infarction, congestive heart failure, peripartum cardiomyopathy, arrhythmias, stroke, thromboembolism, pulmonary edema), and maternal mortality during delivery hospitalizations. Secondary outcomes included the duration of hospital stay, costs, incidence of cesarean sections, preterm births, fetal growth issues, and fetal demise in pregnant patients with IBD.

The researchers sourced discharge data of pregnant patients, both with and without IBD, from the US National Inpatient Sample database from 2009 to 2019. The study included adults aged 18 years and older who were pregnant for at least 20 weeks. Eligibility criteria focused on final discharge records of pregnancies, with IBD diagnoses identified using the International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM codes. The researchers also assessed demographics, hospital characteristics, socioeconomic factors, and various medical conditions.

Further research to identify specific IBD-related factors, such as disease severity, duration, or medication use, contributing to cardiovascular complications will be invaluable for guiding clinical decisions and risk stratification.

The researchers examined 71,361 pregnancies in patients with IBD and compared them with 41,117,443 pregnancies in patients without IBD. Pregnant patients with IBD were generally older (mean [SD] age, 30.55 [0.49] years) compared with individuals without IBD (28.56 [0.02] years; P <.01). Demographically, the majority of women with IBD were White (79.6%) and predominantly treated at large urban hospitals (60.1%), whereas non-IBD patients exhibited a more varied hospital distribution.

The study revealed significantly higher rates of chronic conditions among individuals with IBD, including but not limited to hypertension (odds ratio [OR], 1.19; 95% CI, 1.09-1.30), hyperlipidemia (OR, 1.91; 95% CI, 1.42-2.56), chronic renal failure (OR, 3.28; 95% CI, 2.49-4.85), and depression (OR, 2.74; 95% CI, 2.57-2.92). Conversely, pregnant patients with IBD were less likely to have obesity (OR, 0.89; 95% CI, 0.83-0.95) compared with individuals without IBD.

Between 2009 and 2019, pregnant patients with IBD faced a 37% higher risk for cardiovascular complications compared with individuals without IBD (adjusted OR [aOR], 1.37; 95% CI, 1.29-1.46). This indicates that IBD is an independent risk factor for such complications. These included peripartum cardiomyopathy (aOR, 9.45; 95% CI, 3.86-23.15), cardiac arrhythmias (aOR, 2.03; 95% CI, 1.59-2.60), and hypertensive disorders related to pregnancy (aOR, 1.51; 95% CI, 1.37-1.66). Additionally, pregnancies complicated by IBD carried a 3-fold higher risk of venous thromboembolism (aOR, 3.91; 95% CI, 1.45-10.48).

Study limitations include the cross-sectional design's inability to capture postdischarge cardiovascular events.

The researchers concluded, "[A] collaborative group of experts should deliver comprehensive guidance for pregnant women with IBD, including gastroenterologists, obstetricians and cardiologists."

15. Efficacy of Semaglutide by Sex in Obesity-Related Heart Failure With Preserved Ejection Fraction: STEP-HFpEF Trials

Introduction

Obesity-related heart failure with preserved ejection fraction (HFpEF) is the most prevalent phenotype of HFpEF, representing a persistent and growing source of morbidity and mortality globally.**1** Increasing evidence suggests that visceral adiposity triggers a cascade of local and systemic alterations that actively contribute to both the development and progression of HFpEF,

and these effects are amplified in women.**2-4** Individuals with obesity-related HFpEF experience more severe heart failure (HF) symptoms, worse functional status, diminished quality of life, and poorer clinical outcomes compared with those without obesity.**2-4** Consequently, there is an urgent need for the development of efficacious and safe therapies tailored specifically to address obesity-related HFpEF.

Sex profoundly influences nearly every aspect of HF, spanning from risk factors to clinical presentation, treatment responsiveness, and prognosis.**5** Notably, patients with HFpEF are more commonly women, who often bear a heavier burden of comorbidities and experience worse symptoms and physical limitations compared with men.**1-4**,**6** Despite these challenges, women with HFpEF generally exhibit better survival rates and fewer HF-related hospitalizations.**6** Variances in ventricular structure and function (with smaller left ventricular cavities and higher ejection fraction), and responsiveness to elevated left ventricular filling pressures have been observed between women and men.**7**,**8**

Women have been shown to have smaller left ventricular cavity size. Body composition and adipose distribution vary between women and men, which may also affect the impact of therapies targeting excess body fat.**2** One prevailing theory suggests that 1 of the primary drivers behind adverse clinical manifestations of HFpEF in women is related to differences in the quantity and distribution of visceral adiposity, which can trigger aberrant epicardial and endothelial inflammation.**9** Moreover, the relationship between blood and plasma volume augmentation with increasing body weight is notably steeper in women than in men.**9** Sex differences have also been observed in responses to certain treatments. For example, in the PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction) study, a more favorable effect of sacubitril/valsartan on the primary endpoint (total HF hospitalizations and cardiovascular death) was observed in women than in men with HFpEF.**10**

The majority of evidence on sex disparities in HFpEF epidemiology and clinical progression has been drawn from studies not specifically targeting patients with obesity-related HFpEF. Consequently, there is a scarcity of data on potential variations in baseline characteristics, outcomes, and responses to pharmacologic treatments by sex within this phenotype. This gap is particularly crucial given clear indications that obesity serves as a more potent risk factor for HF in women compared with men,**11** and the demonstration in prior trials that women living with obesity tend to lose more weight with antiobesity agents than their male counterparts.**12**,**13**

In the STEP-HFpEF (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity) and STEP-HFpEF DM (Research Study to Look at How Well Semaglutide Works in People Living With Heart Failure, Obesity and Type 2 Diabetes) trials (which comprise the STEP-HFpEF program),**14-18** once-weekly semaglutide 2.4 mg improved HF-related symptoms, physical limitations, and exercise function, and reduced weight and biomarkers of inflammation in individuals with obesity-related HFpEF. This prespecified pooled patient-level analysis aimed to evaluate the influence of sex on baseline characteristics, as well as the effects of semaglutide vs placebo on the key trial endpoints in the STEP-HFpEF program according to sex.

Methods

Study and program design

This analysis was prespecified within the framework of the randomized, international, multicenter, double-blind, placebo-controlled STEP-HFpEF program. The program consisted of 2 trials: STEP-HFpEF (for patients with obesity-related HFpEF without type 2 diabetes; **NCT04788511**) and STEP-HFpEF DM (for patients with obesity-related HFpEF and type 2 diabetes; **NCT04916470**). The design and primary outcomes of the individual trials, as well as the overall program, were previously published.**14**,**16**,**17**,**19** The participants were recruited from 129 sites

across 18 countries in Asia, Europe, North America, and South America. All investigators were encouraged to enroll diverse populations including ethnically diverse subjects and women. As such, about 50% of the subjects enrolled in the trial are women. The steering committee, comprising academic members and representatives from the sponsor (Novo Nordisk), designed both trials and oversaw academic publications. A global expert panel provided input on academic, medical, and operational aspects in each country. The steering committee and national leader membership represent geographical and gender diversity. Each study site obtained Institutional Review Board/ethics committee approval,**16**,**18** and all patients provided informed consent. Novo Nordisk sponsored the program.

Study program participants and randomization

Eligible participants had a left ventricular ejection fraction (LVEF) ≥45%, a body mass index (BMI) of ≥30 kg/m2, NYHA functional class II to IV, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) <90 points, 6-minute walking distance (6MWD) of at least 100 m, and at least 1 of the following: elevated filling pressures (invasively measured), elevated natriuretic peptide levels plus structural echocardiographic abnormalities, or a history of HF hospitalization in the preceding 12 months plus ongoing diuretic treatment and/or echocardiographic abnormalities. Key exclusion criteria included prior or planned bariatric surgery, significant recent weight change, or high systolic blood pressure. Patients with uncontrolled diabetic retinopathy or maculopathy were excluded from STEP-HFpEF DM. Eligible participants were randomized 1:1 to receive a once-weekly subcutaneous target dose of semaglutide 2.4 mg or matching placebo in addition to standard care for 52 weeks. Randomization was stratified by BMI (<35 kg/m2 vs ≥35 kg/m2). Semaglutide or placebo was added to background glucose-lowering medications for patients with type 2 diabetes in STEP-HFpEF DM, with treatment adjustments at the investigator's discretion.

Efficacy and safety outcomes

The main objective of this analysis was to assess the effects of semaglutide 2.4 mg once weekly vs placebo on the dual primary and confirmatory secondary outcomes in the STEP-HFpEF program by sex. The dual primary endpoints were changes in KCCQ-CSS and percent change in body weight from baseline to 52 weeks. Confirmatory secondary endpoints included changes in 6MWD, a hierarchical composite endpoint (which included all-cause death from baseline to week 57; number and timing of HF events [adjudicated hospitalizations for HF or urgent visits requiring intravenous therapy, baseline to week 57]; differences ≥15, ≥10, and ≥5 points in the KCCQ-CSS change from baseline to week 52; and a difference of a least 30 m in the 6MWD change from baseline to week 52), and changes in C-reactive protein (CRP) levels from baseline to 52 weeks. Changes in the systolic blood pressure, waist circumference, and levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) between baseline and week 52 by sex were also evaluated as supportive secondary and select exploratory endpoints in this analysis. Finally, as exploratory endpoints, we also evaluated the changes in all key summary (KCCQ-CSS, Overall Summary Score, and Total Symptom Score) and individual (Symptom Burden Score, Symptom Frequency Score, Physical Limitation Score, Social Limitations Score, and Quality of Life Score) KCCQ domains between baseline and 52 weeks by sex. Safety endpoints included serious adverse events (SAEs) and SAEs leading to discontinuation and deaths, evaluated within the sex subgroups.

Statistical analysis

Baseline characteristics were evaluated according to sex. Continuous variables were compared using Student's *t*-test, and categorical variables were compared using chi-square or Fisher exact test. The effects of semaglutide vs placebo were examined using the full analysis set (all randomized participants according to the intention-to-treat principle, while in-trial regardless of treatment discontinuation). The effects of semaglutide (vs placebo) by sex were also assessed across key subgroups including age (≤69 years or >69 years), BMI (<35 kg/m2 or ≥35 kg/m2), LVEF (<57% or

≥57%), and CRP levels (<3.7 mg/L or ≥3.7 mg/L). Analyses of continuous and other endpoints were performed using analysis of covariance models adjusted for the baseline value of the relevant continuous outcome variable, with treatment, trial, and BMI (<35 kg/m2 or ≥35 kg/m2) as fixed factors using 1,000 imputations; analyses also included an interaction term between treatment and sex subgroup. Estimates were then combined using Rubin's rule. For the analyses of change in KCCQ-CSS and 6MWD, missing observations at week 52 caused by cardiovascular death or previous HF events were single imputed to the lowest observed value across both treatment arms and visits. Missing values caused by other reasons were multiple imputed from retrieved participants in the same randomized treatment arm. For other endpoints, missing observations at week 52 were multiple imputed irrespective of death or prior HF events using the same imputation method. Interaction *P* values were derived from an F-test of equality between the treatment differences across the 2 groups.

Analyses of the hierarchical composite endpoint (win ratio) were performed stratified by sex, based on direct comparisons of each participant randomized to semaglutide vs each participant randomized to placebo. For each of the participant pairs, a "treatment winner" based on similar observation time was declared based on the endpoint hierarchy. The win ratio (ie, the proportion of winners randomized to semaglutide divided by the winners randomized to placebo) was estimated independently by sex (using 1,000 imputations as described in the previous text). Test for equality for the win ratio was performed using Cochran's Q test.

For the responder analyses, we examined the proportions of participants by sex (on the basis of the observed [ie, nonimputed] data) who experienced a ≥5-point deterioration as well as ≥5-, ≥10-, ≥15-, and ≥20-point improvement across all key KCCQ domains (corresponding to at least small, at least moderate, large, and very large improvements) in semaglutide- and placebo-treated patients. For KCCQ-CSS, we also constructed the cumulative response curves by sex that plotted observed changes in KCCQ-CSS scores between baseline and week 52 against the cumulative proportions of

participants in the semaglutide and placebo groups experiencing those changes (≥20-point improvement; ≥10-point worsening). Logistic regression models were then used to calculate the ORs and corresponding 95% CIs for semaglutide effects on the likelihood of ≥5-point deterioration, as well as ≥5-, ≥10-, ≥15-, and ≥20-point improvement across all key KCCQ domains, with 1,000 multiple imputations to account for missing data, adjusted for the baseline values for the relevant outcome variable, trial, and BMI group (the stratification factor). Safety endpoints by sex were analyzed using the safety analysis set (all randomized participants exposed to at least 1 dose of randomized treatment) and either on-treatment or in-trial data sets depending on the type of safety event. No adjustment for multiple testing was performed. A 2-sided *P* value of <0.05 was considered significant. Results are presented as estimated changes from baseline to week 52 for continuous endpoints, a win ratio (for the hierarchical composite endpoint), or an OR (for responder analyses), with a 95% CI and a 2-sided *P* value. NT-proBNP and CRP were log-transformed, and hence, treatment ratios with the corresponding 95% CIs at week 52 are reported. Statistical analyses were performed by the independent statistical group at Saint Luke's Mid America Heart Institute, in collaboration with Novo Nordisk, using SAS version 9.4 (SAS/STAT version 15.1). All analyses were performed on the anonymized data.

Results

Baseline differences in women and men with HFpEF

A total of 1,145 patients from the 2 trials (STEP-HFpEF, n = 529; STEP-HFpEF DM, n = 616) were included in the analysis, of whom 570 (49.7%) were women (**Table 1**). The age distribution and ethnicity were comparable between women and men. Women had lower body weight and waist circumference, but higher BMI (**Table 1**). Systolic blood pressure and history of hypertension were similar across sexes. Women had higher LVEF, presented with worse symptoms and physical limitations: a higher

proportion of women than men were classified as NYHA functional class III to IV, and baseline KCCQ-CSS and 6MWD were lower in women.

Table 1Baseline Characteristics of Patients from the Pooled STEP-HFpEF and STEP-HFpEF DM Trials by Sex Characteristics	**Total (N = 1,145a)**	**Women (n = 570)**	**Men (n = 575)**	***P* Value**
Age, y				
<65	368 (32.1)	172 (30.2)	196 (34.1)	
65-79	666 (58.2)	334 (58.6)	332 (57.7)	0.125
≥80	111 (9.7)	64 (11.2)	47 (8.2)	
Raceb				
Asian	76 (6.6)	41 (7.2)	35 (6.1)	
Black or African American	39 (3.4)	24 (4.2)	15 (2.6)	0.397
Other	4 (0.3)	2 (0.4)	2 (0.3)	
White	1,026 (89.6)	503 (88.2)	523 (91.0)	
Body weight, kg	103.7 (91.3-119.0)	96.0 (86.0-108.6)	111.5 (99.6-125.4)	<0.001
BMI,c kg/m2	38.0 (34.6-42.6)	38.8 (35.3-43.7)	37.1 (34.0-41.8)	<0.001
Waist circumference, cm	120.0 (111.0-129.0)	115.4 (108.0-124.5)	123.8 (116.0-133.0)	<0.001
Systolic blood pressure, mm Hg	133.0 (123.0-	135.0 (123.0-	133.0 (122.0-	0.391

Table 1Baseline Characteristics of Patients from the Pooled STEP-HFpEF and STEP-HFpEF DM Trials by Sex Characteristics	**Total (N = 1,145a)**	**Women (n = 570)**	**Men (n = 575)**	***P* Value**
	144.0)	144.0)	144.0)	
NYHA functional class				
II	785 (68.6)	360 (63.2)	425 (73.9)	
III	358 (31.3)	209 (36.7)	149 (25.9)	<0.001
IV	2 (0.2)	1 (0.2)	1 (0.2)	
LVEF, %	57.0 (50.0-60.0)	60.0 (54.0-61.0)	55.0 (50.0-60.0)	<0.001
KCCQ-CSS, points	58.9 (43.2-72.4)	54.7 (38.5-67.2)	63.0 (48.4-76.0)	<0.001
6MWD, m	294.8 (220.0-368.0)	270.5 (200.0-344.0)	322.1 (241.7-387.0)	<0.001
CRP, mg/L	3.7 (1.8-8.1)	4.4 (2.1-9.4)	3.0 (1.6-6.8)	0.002
NT-proBNP, pg/mL	477.8 (236.8-1,015.7)	436.4 (237.6-921.0)	522.6 (236.8-1,120.6)	0.36
Comorbidities at screening				
Hypertension	959 (83.8)	482 (84.6)	477 (83.0)	0.461
Atrial fibrillation	518 (45.2)	227 (39.8)	291 (50.6)	<0.001

Table 1Baseline Characteristics of Patients from the Pooled STEP-HFpEF and STEP-HFpEF DM Trials by Sex Characteristics	**Total (N = 1,145a)**	**Women (n = 570)**	**Men (n = 575)**	***P* Value**
Obstructive sleep apnea	119 (10.4)	48 (8.4)	71 (12.3)	0.029
Coronary artery disease	453 (39.6)	181 (31.8)	272 (47.3)	<0.001
Diabetesd	616 (53.8)	273 (47.9)	343 (59.7)	<0.001
Concomitant medications				
Diuretics	925 (80.8)	456 (80.0)	469 (81.6)	0.501
Loop diuretics	702 (61.3)	348 (61.1)	354 (61.6)	0.858
Thiazides	175 (15.3)	88 (15.4)	87 (15.1)	0.884
Beta-blockers	928 (81.0)	456 (80.0)	472 (82.1)	0.367
SGLT2i	221 (19.3)	83 (14.6)	138 (24.0)	<0.001
MRA	384 (33.5)	183 (32.1)	201 (35.0)	0.306
ACEI/ARB (ARNI)	899 (78.5)	428 (75.1)	471 (81.9)	0.004
ARNI	58 (5.1)	23 (4.0)	35 (6.1)	0.113
Insulin and analogues	128 (11.2)	58 (10.2)	70 (12.2)	0.283
Sulfonylureas	106 (9.3)	51 (8.9)	57 (9.9)	0.576

Table 1Baseline Characteristics of Patients from the Pooled STEP-HFpEF and STEP-HFpEF DM Trials by Sex Characteristics	**Total (N = 1,145a)**	**Women (n = 570)**	**Men (n = 575)**	***P* Value**
DPP-4 inhibitors	92 (8.0)	40 (7.0)	52 (9.0)	0.207

Values are n (%) or median (Q1-Q3) and are from the full analysis set. Percentages may not equal 100% because of rounding. Continuous variables were compared using Student's *t*-test. Categorical variables were compared using chi-square or Fisher exact test.

6MWD = 6-minute walk distance; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; CRP = C-reactive protein; DM = diabetes mellitus; DPP-4 = dipeptidyl peptidase 4; HFpEF = heart failure with preserved ejection fraction; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro–B-type natriuretic peptide; SGLT2i = sodium–glucose cotransporter 2 inhibitor.

a A total of 1,146 participants were randomized; however, 1 participant was randomized in error such that the full analysis set comprises 1,145 participants.

b Race was reported by the investigator.

c Body mass index (BMI) is the weight (kg) divided by the square of the height (m).

d Diabetes was an exclusion criterion in the STEP-HFpEF (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity) trial; therefore, the data shown are from the STEP-HFpEF DM (Research Study to Look at How Well Semaglutide Works in People Living With Heart Failure, Obesity and Type 2 Diabetes) trial only.

Women had higher baseline CRP levels than men with HFpEF, whereas NT-proBNP levels were not significantly different between the sexes. Women were less likely to have a history of coronary artery disease or atrial fibrillation. The use of loop diuretic agents and mineralocorticoid receptor antagonists did not differ between groups, but women were less likely to be treated with sodium–glucose cotransporter 2 inhibitors (SGLT2i) or inhibitors of the renin-angiotensin system (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker).

Efficacy of semaglutide vs placebo by sex

Compared with placebo, semaglutide improved KCCQ-CSS similarly in both sexes; the adjusted mean difference was +7.5 points (95% CI: 4.3-10.6 points) in men and +7.6 points (95% CI: 4.5-10.7 points) in women (*P* interaction = 0.944) at 52 weeks (**Table 2**). The improvement in KCCQ-CSS emerged early after treatment initiation and was amplified during the trial, with a pattern that was consistent in both sexes (**Figure 1**). The observed benefits on KCCQ-CSS were seen consistently in both sexes across key subgroups by age, BMI, LVEF, and CRP (**Supplemental Table 1**, **Supplemental Figure 1**). Semaglutide led to a significant reduction in body weight in both sex subgroups but resulted in a ~ 2.5% greater weight loss in women compared with men (*P* interaction = 0.006) (**Table 2**). Semaglutide improved 6MWD, resulted in a greater number of wins vs placebo for the hierarchical composite endpoint, and reduced CRP and NT-proBNP in both men and women, with no significant heterogeneity of treatment benefits (**Table 2**).

Table 2Effect of Semaglutide Compared With Placebo on Outcomes by Sex	**Women (n = 570)**		**Men (n = 575)**		
	Semaglutide 2.4 mg (n = 277)	**Placebo (n = 293)**	**Semaglutide 2.4 mg (n = 296)**	**Placebo (n = 279)**	***P* Value**

Table 2Effect of Semaglutide Compared With Placebo on Outcomes by Sex	**Women (n = 570)**		**Men (n = 575)**		
	Semaglutide 2.4 mg (n = 277)	**Placebo (n = 293)**	**Semaglutide 2.4 mg (n = 296)**	**Placebo (n = 279)**	***P* Value**
Dual primary endpoints					
Change in KCCQ-CSS at 52 wks, points	n = 254 14.5 (12.2–16.7)	n = 261 6.9 (4.7–9.1)	n = 270 15.5 (13.3–17.7)	n = 248 8.1 (5.8–10.3)	
Adjusted mean difference, points	7.6 (4.5–10.7)		7.5 (4.3–10.6)		0.944
Change in body weight at 52 wks, %	n = 257 −12.6 (−13.5 to −11.7)	n = 268 −3.0 (−3.9 to −2.1)	n = 275 −10.2 (−11.1 to −9.3)	n = 252 −3.0 (−4.0 to −2.1)	
Adjusted mean difference, %	−9.6 (−10.9 to −8.4)		−7.2 (−8.4 to −6.0)		0.006
Confirmatory secondary endpoints					
Change in 6MWD at 52 wks, m	n = 252 12.0 (4.1–19.9)	n = 251 −0.1 (−8.0 to 8.1)	n = 269 21.3 (13.5–29.1)	n = 239 −0.7 (−8.8 to 7.3)	
Adjusted mean difference, m	11.9 (0.7–23.1)		22.0 (11.0–33.1)		0.207
Hierarchical composite endpoint, win	1.58 (1.27–1.98)		1.75 (1.40–2.18)		0.658

Table 2Effect of Semaglutide Compared With Placebo on Outcomes by Sex	**Women (n = 570)**		**Men (n = 575)**		
	Semaglutide 2.4 mg (n = 277)	**Placebo (n = 293)**	**Semaglutide 2.4 mg (n = 296)**	**Placebo (n = 279)**	***P* Value**
ratio					
CRP ratio at 52 wks	n = 253 0.54 (0.48–0.62)	n = 268 0.92 (0.81–1.03)	n = 274 0.60 (0.53–0.69)	n = 252 0.88 (0.77–1.00)	
Treatment ratio	0.59 (0.50–0.70)		0.69 (0.57–0.82)		0.232
Supportive secondary and exploratory endpoints					
Change in systolic blood pressure at 52 wks, mm Hg	n = 257 −5.6 (−7.5 to −3.6)	n = 268 −1.7 (−3.7 to 0.4)	n = 275 −3.7 (−5.6 to −1.8)	n = 253 −1.8 (−4.0 to 0.4)	
Adjusted mean difference, mm Hg	−3.9 (−6.7 to −1.1)		−1.9 (−4.8 to 1.0)		0.335
Change in waist circumference at 52 wks, cm	n = 257 −11.8 (−12.8 to −10.8)	n = 266 −3.7 (−4.7 to −2.6)	n = 273 −8.8 (−9.8 to −7.8)	n = 251 −1.5 (−2.6 to −0.4)	
Adjusted mean difference, cm	−8.1 (−9.5 to −6.7)		−7.3 (−8.8 to −5.8)		0.445
Change in KCCQ Overall	n = 254 14.3 (12.0–	n = 261 7.3 (5.1–	n = 270 15.5 (13.3–	n = 248 7.7 (5.5–	

Table 2Effect of Semaglutide Compared With Placebo on Outcomes by Sex	**Women (n = 570)**		**Men (n = 575)**		
	Semaglutide 2.4 mg (n = 277)	**Placebo (n = 293)**	**Semaglutide 2.4 mg (n = 296)**	**Placebo (n = 279)**	***P* Value**
Summary Score at 52 wks, points	16.5)	9.5)	17.7)	9.9)	
Adjusted mean difference, points	7.0 (3.9–10.1)		7.8 (4.7–10.9)		0.707
NT-proBNP ratio at 52 wks	n = 255 0.76 (0.69–0.85)	n = 268 0.96 (0.86–1.07)	n = 274 0.79 (0.72–0.88)	n = 252 0.95 (0.84–1.06)	
Treatment ratio	0.80 (0.69–0.93)		0.84 (0.72–0.98)		0.662

Data are from the in-trial period for the full analysis set. Patient numbers for each endpoint indicate the number assessed. Values in parentheses are 95% CIs. *P* values are for interactions between treatment and sex. Abbreviations as in **Table 1**.

Change in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score in Women and Men

Change in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score is from baseline to week 52 in (A) women and (B) men. Observed data are from the in-trial period. Error bars are ± SEM. Numbers shown in the lower panel are subjects contributing to the mean. aEstimated means are from the analysis of covariance. ETD = estimated treatment difference.

Supplemental Table 1 depicts the efficacy of semaglutide vs placebo across KCCQ domains by sex. Over 52 weeks, treatment with semaglutide (vs placebo) consistently improved all KCCQ summary and individual domains in both sexes with no heterogeneity noted. The efficacy of semaglutide in lowering systolic blood pressure and waist circumference was also similar by sex.

From the logistic regression model for responder analysis, semaglutide- vs placebo-treated patients had a significantly lower odds of ≥5-points deterioration: 0.49 (95% CI: 0.35-0.68; $P < 0.001$), with no heterogeneity by sex. Additionally, semaglutide- vs placebo-treated patients had significantly higher odds of ≥5-point (OR: 2.10; 95% CI: 1.61-2.73; $P < 0.001$), ≥10-point (OR: 2.07; 95% CI: 1.61-2.69; $P < 0.001$), ≥15-point (OR: 2.03; 95% CI: 1.55-2.65; $P < 0.001$), and ≥20-point (OR: 2.36; 95% CI: 1.76-3.17; $P < 0.001$) improvement in KCCQ-CSS consistently in women and men (**Supplemental Figure 2**).

The cumulative response analysis showed continuous separation of KCCQ-CSS curves in favor of semaglutide vs placebo across the entire range of KCCQ change between baseline and week 52 in men and women, respectively (**Figure 2**). In women, 39.0% of patients treated with semaglutide experienced an increase in KCCQ-CSS of ≥20 points, compared with 25.7% treated with placebo. The corresponding numbers in men were 35.6% and 21.0%, respectively. Conversely, 5.9% of female patients treated with semaglutide experienced a decrease in KCCQ-CSS of ≥10 points compared with 12.6% in the placebo group. The corresponding numbers for men were 7.4% and 15.3%, respectively.

Change in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (Cumulative Response Curves) in Women and Men

Change in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) is from baseline to week 52 in (A) women and (B) men. Observed data are from the in-trial period for the full analysis set. The graph

shows cumulative frequency distributions of change from baseline in KCCQ-CSS. To interpret this graph, select a change in KCCQ-CSS on the x-axis and find the corresponding proportion of semaglutide 2.4 mg and placebo participants who achieved that degree of improvement or worsening on the y-axis. For example, note that in panel A, the vertical line arising from 20-point improvement intersects with semaglutide and placebo curves at 64.4% and 79.0%, respectively. Therefore, 35.6% and 21.0% in the semaglutide and placebo groups achieved a ≥20-point improvement, respectively.

Safety outcomes

There were fewer SAEs, and serious cardiac disorders, in women and men treated with semaglutide vs placebo (**Supplemental Table 2**). Gastrointestinal SAEs and SAEs leading to premature discontinuation were similar between treatment groups by sex.

Discussion

In this prespecified patient-level pooled analysis of STEP-HFpEF and STEP-HFpEF DM (STEP-HFpEF program), we observed notable differences between women and men with obesity-related HFpEF. Women exhibited a higher BMI and presented with more severe HF-related symptoms, physical limitations, and reduced exercise tolerance compared with men despite higher LVEF. Levels of inflammation, as measured by CRP, were higher in women, although women had lower rates of comorbid conditions such as atrial fibrillation and coronary artery disease compared with men. The lower KCCQ-CSS and higher CRP levels observed in women compared with men at baseline indicate a significant gap and highlight the need to better understand and address the nature of such disparities. Semaglutide led to greater weight loss in women compared with men, but despite differential weight loss and key differences in baseline characteristics by sex, we found no significant treatment-by-sex interactions for any of the HF outcomes assessed. Semaglutide 2.4 mg once weekly, compared with placebo, demonstrated consistent and large improvements across all domains of

KCCQ, increased 6MWD, and reduced CRP and NT-proBNP levels, irrespective of sex. Responder analyses revealed similar proportions of patients experiencing at least 5-, 10-, 15-, and 20-point improvements in KCCQ-CSS scores with semaglutide compared with placebo, regardless of sex. Furthermore, improvements in KCCQ-CSS showed no treatment heterogeneity by age, BMI, LVEF, or CRP levels in either sex for semaglutide.

Despite considerable research into sex-based differences in the epidemiology, pathophysiology, and clinical course of HFpEF, there is still a significant gap in understanding such variances within the context of the obesity phenotype of HFpEF. Consistent with previous HFpEF trials, our findings indicate that women with obesity-related HFpEF experience more severe HF-related symptoms compared with men.**6**,**20** The mechanisms underlying these differences are complex and likely multifactorial. One proposed explanation is that increased adiposity in women serves as a critical causal factor.**4** Indeed, prior studies have shown that women with obesity-related HFpEF exhibit significantly higher levels of visceral adiposity, which can disproportionately impact exercise hemodynamics and exacerbate HF symptoms compared with men.**4**,**9** Visceral adiposity is thought to act as a reservoir for the synthesis and release of various adipocytokines and neurohormones, promoting local and systemic inflammation, sodium retention, and plasma volume expansion.**9** It has been theorized that the higher symptom burden in women may stem from a more pronounced increase in exercise pulmonary capillary wedge pressure with elevated plasma and blood volume compared with men.**9**

Furthermore, visceral adiposity is implicated as a key driver of heightened inflammation and microvascular endothelial dysfunction, both prevalent in women with HFpEF. The findings of greater inflammation in women with obesity-related HFpEF has not been previously described and suggests a potentially important sex-difference in pathophysiology. Systemic inflammation was reduced to a similar extent in both women and men, but because women had higher CRP at baseline, they may have greater residual inflammation even following treatment. Increased inflammation is believed

to contribute to oxidative stress and impair myocardial energetics,**9** potentially explaining the exacerbated symptoms observed in women. Finally, excessive adiposity in women, as opposed to men, may impose greater extrinsic constraints on the heart, hindering venous return and predisposing individuals to hemodynamic deterioration.**21**

The sex-based differences in baseline demographics observed in the STEP program exhibit both similarities and differences compared with previous HFpEF trials. Notably, the proportion of women enrolled (~ 50%) aligns with recent trials investigating SGLT2i in HFpEF.**22**,**23** In contrast to earlier HFpEF studies where women tended to be older than men, the present study found no such age disparity. This may relate to the fact that patients with the obesity phenotype of HFpEF are, on average, a decade younger than those with HFpEF without obesity.**3**,**24** Consistent with prior HFpEF studies, women had lower rates of coronary artery disease. However, unlike previous studies, we found that women had similar rates of hypertension and diuretic use and less atrial fibrillation compared with men. The lower rates of atrial fibrillation despite higher BMI in women is an interesting and unexpected finding. Because atrial fibrillation is a marker of left atrial myopathy, these data may indicate that more female participants had a more typical isolated obesity phenotype, whereas more male participants had left atrial myopathy HFpEF complicated by an increase in BMI. Interestingly, women were also less likely to receive an SGLT2i or inhibitors of the renin-angiotensin system than men. Similarly, in line with previous HFpEF trials, women in this study presented with more severe symptoms despite having higher LVEF. One proposed explanation is that because women typically have lower left ventricular volumes than men, they may rely more heavily on a higher ejection fraction to maintain stroke volume and cardiac output, potentially explaining the observed higher LVEF.**25** Ventricular volume contracture in this setting may further exacerbate elevation in cardiac filling pressures with higher LVEF,**26** especially because volume expansion is greater in women with HFpEF and more visceral adiposity.**9** The BMI among women in the STEP-

HFpEF program was markedly higher than that reported in recently completed HFpEF trials. For instance, in the EMPEROR-Preserved (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction) trial, women had a BMI of approximately ~ 30 kg/m2,**22** compared with ~ 39 kg/m2 noted in the present study. This difference in BMI levels may contribute to the lower levels of NT-proBNP observed relative to previous HFpEF trials, because there is an inverse relationship between BMI and NT-proBNP levels.**3**,**27**

Previous pharmacologic studies in HFpEF have suggested potential interactions between sex and treatment efficacy. For instance, in the PARAGON-HF trial, a subgroup analysis indicated that women responded more favorably to sacubitril/valsartan than men.**10** Similarly, a post hoc analysis of the TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function) trial suggested that spironolactone therapy reduced all-cause mortality in women with HFpEF but not in men.**28** However, no such sex-treatment interaction has been observed with empagliflozin or dapagliflozin in patients with HFpEF, although the obesity-related HFpEF phenotype was not specifically targeted in these trials.

The consistency and magnitude of benefit observed with semaglutide in the STEP-HFpEF program, regardless of sex, are quite notable. Although direct comparisons between trials can be challenging, we noted improvements in KCCQ-CSS of nearly +8 points at 52 weeks in both men and women. In contrast, in the EMPEROR-Preserved trial, empagliflozin improved KCCQ-CSS by approximately +2.5 points in women and +2.2 points in men. Similar results were observed in the DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure) trial with dapagliflozin, though KCCQ benefits were greater in patients with higher BMI.**29** Furthermore, neither SGLT2i nor mineralocorticoid receptor antagonists have demonstrated significant reductions in CRP in HFpEF, unlike the observations made in the STEP-HFpEF program.**15** SGLT2i cause a modest but similar reduction in weight in men and women of

approximately 1.5 kg. In STEP-HFpEF, although we observed clinically meaningful, significant reductions in weight with semaglutide in both sexes, women had an augmented response. This is consistent with what has been demonstrated previously with semaglutide (and other incretin-based therapies) in other trials.**12**,**30** The exact mechanism for this, however, remains unclear. Of note, the impact of semaglutide on HF outcomes was similar between men and women despite greater weight loss in women. This suggests that mechanisms beyond weight loss may play a role in mediating the effects of semaglutide in obesity-related HFpEF.

Study limitations

The results of this analysis must be interpreted within the context of potential limitations.

1. The key objectives of the STEP-HFpEF program were to evaluate the effects of semaglutide on HF-related symptoms, physical limitations, and exercise function, and it was not designed to assess HF events, although numerically fewer adjudicated events were reported with semaglutide than placebo in the program.**17**

2. Alternative anthropometric assessments of visceral adiposity were not available. Furthermore, sex- and ethnicity-based thresholds for adiposity were not employed, potentially limiting generalizability of these data.

3. Few non-White patients were enrolled, which also limits broad generalizability.

4. There was an imbalance in SGLT2i use in women vs men; however, as previously reported, the effects of semaglutide vs placebo on KCCQ-CSS were consistent regardless of background SGLT2i use.**17**

5. Mechanistic insights regarding body composition, skeletal/visceral fat, microvascular function, and extracardiac adiposity were not available.

6. Finally, analyses were confined to biologic sex and the impact of gender

was not characterized.

Conclusions

In patients with obesity-related HFpEF, women have greater symptom severity, greater exercise limitation, and more severe systemic inflammation than men. Treatment with semaglutide reduced body weight in both women and men but resulted in greater weight loss in women. Despite greater reductions in weight in women than men, semaglutide produced similar, clinically meaningful improvements in HF-related symptoms, physical limitations, and exercise function, along with reductions in inflammation and natriuretic peptides, regardless of sex.

16. Under Pressure to Optimize the Cardiac Care of Breast Cancer Survivors

Introduction

Hypertension is recognized as one of the most prevalent, modifiable, and targetable risk factors to affect adverse cardiovascular (CV) outcomes in breast cancer survivors.**1**,**2** The American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guidelines emphasize health promotion in breast cancer survivors without specific recommendations for blood pressure targets.**3** According to the European Society of Cardiology (ESC) Cardio-Oncology Guidelines, treatment for asymptomatic hypertension should be based on different patient scenarios depending on stage of disease and prognosis.**4** The ESC guidelines specify that initiation of blood pressure treatment for cancer survivors should be considered for systolic blood pressure (SBP) at 135 to 140 mm Hg. Is this an optimal blood pressure target? Or should we be lowering blood pressure goals for cancer survivors to a similar range as patients without cancer? Should high-risk cancer survivors exposed to cardiotoxic treatment be managed differently? Unfortunately, major clinical trials that targeted SBP, such as SPRINT (Systolic Blood Pressure Intervention Trial), excluded

patients with active cancer, and it is not clear how many patients with a history of cancer were enrolled.**5** As the breast cancer survivor population ages, CV disease becomes the primary driver of morbidity and mortality. We must better understand the contribution of hypertension to increased CV disease in breast cancer survivors and optimal blood pressure goals for these patients.

In this issue of *JACC: Advances*, Leedy et al present the results of The Pathways Heart Study,**6** which sought to address these questions by examining the associations between blood pressure and three CV outcomes (ischemic heart disease [IHD], stroke, and incident heart failure/cardiomyopathy) in female breast cancer survivors. In this large prospective cohort study with a median follow-up of 9.6 years, female breast cancer survivors were matched 5:1 to controls on age, race, and ethnicity. They measured time-averaged SBP and diastolic blood pressure (DBP) from cancer diagnosis until the first incident CV outcome. Blood pressure groups were divided into continuous and categorical variables by 10-unit increments from 100 to 160 mm Hg for SBP and <60 to 90 mm Hg for DBP. They found a positive association between SBP and IHD and stroke, a J-shaped association between DBP and IHD and stroke, and a U-shaped association between SBP and DBP and incident heart failure/cardiomyopathy. There were no differences between these blood pressure associations when female breast cancer survivors were compared to controls.

These complex associations between blood pressure and CV outcomes draw attention to the extremes of high and low blood pressure and individualizing blood pressure to CV outcomes. Elevated SBP and elevated/low DBP are associated with risk of IHD and stroke. Elevated/low SBP and DBP are associated with risk of heart failure/cardiomyopathy. This U-shaped blood pressure relationship for heart failure/cardiomyopathy has been previously reported in patients without cancer in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial).**7** These results should be considered in the design of future prospective studies of hypertension.

Should these blood pressure targets also be extended beyond breast cancer survivors to patients with active cancer? Notably, the ESC guidelines recommend more lenient hypertension treatment targets for patients during treatment with either curable cancer or metastatic disease. Arguably, metastatic HER2+ breast cancer patients should be treated like breast cancer "survivors" due to good prognosis and increased survival from the success of targeted anti-HER2 therapies. However, further research is needed regarding optimal blood pressure for all breast cancer patients, including those with metastatic disease or undergoing active cancer treatment, to reduce potential late-effects of cancer treatment related to elevated hypertension. Elevated blood pressure during breast cancer therapy has been associated with decreased left ventricular ejection fraction and global longitudinal strain, which increase the risk of CV late effects of cancer treatment.**8** Optimizing blood pressure control during active breast cancer therapies can also lead to better long-term tolerability of cancer therapies and thus potentially improved treatment outcomes.

Another reason to control blood pressure in breast cancer survivors is the research demonstrating a relationship between hypertension and the development of breast cancer. Several observational studies have demonstrated an association between hypertension with risk of breast cancer in postmenopausal women. A large meta-analysis demonstrated a 15% higher risk of breast cancer in adults with hypertension.**9** While the mechanisms driving associations between hypertension and breast cancer risk are not well established, it is plausible that hypertension may also increase risk of breast cancer recurrence. A study by Lorona et al**10** found that women with hypertension treated with specific antihypertensive medications were at increased risk of breast cancer recurrence. Additional prospective studies are needed to understand the relationship between hypertension as well as cardiac comorbidities such as obesity and diabetes among breast cancer survivors and risk of cancer outcomes.

Although promotion of cardiac health and prevention of cardiotoxicity are emphasized in the American Cancer Society/American Society of Clinical

Oncology Breast Cancer Survivorship Guidelines, the primary focus is on lifestyle modifications such as weight management and exercise. Often clinicians are biased in lenient management of blood pressure in patients with cancer. However, as cancer survivors are living longer, guidelines for prevention of chronic diseases in this population must also adapt and change. Prospective research should be ongoing to determine whether optimal blood pressure targets vary for breast cancer patients along the cancer care continuum exposed to additional clinical risk factors such as left-sided radiation and new/specific anticancer therapies. Patients with cancer and a history of cancer should not be excluded from randomized clinical trials for hypertension. Education of patients, primary care physicians, oncologists, and cardiologists on the importance of optimizing blood pressure in cancer survivors is essential. Let us ensure that emphasizing a healthy lifestyle in breast cancer survivors incorporates optimal targets for blood pressure.

17. Patient Perceptions and Knowledge Surrounding Pregnancy After Heart Transplantation

BACKGROUND

More women of childbearing age are surviving after heart transplantation (HT), many of whom have a desire to become pregnant. Limited data exist evaluating patients' perspectives, receipt of counseling, and knowledge surrounding contraception, pregnancy, breastfeeding, and medication safety after HT.

METHODS

We conducted a voluntary, confidential, web-based cross-sectional survey of women who were childbearing age (defined as 18-45 years) at the time of HT. Transplants occurred between January 2005 and January 2020. Surveys were conducted across 6 high-volume HT centers in the United States.

RESULTS

There were 64 responses from women who were of childbearing age at the time of HT. Twenty-five women (39.1%) were pregnant before HT, and 6

(9.4%) women reported at least 1 pregnancy post-transplant. Fifty-three percent (n=34) reported they did not receive enough information on post-HT pregnancy before listing for HT, and 26% (n=16) did not discuss their ability to become pregnant with their care team before proceeding with HT. Following HT, 44% (n=28) still felt that they had not received enough information regarding pregnancy. The majority of women (n=49, 77%) had discussed contraception to prevent unplanned pregnancy with their transplant team. Twenty percent (n=13) reported that pregnancy was never safe after transplantation based on the information they had received from their transplant providers.

CONCLUSIONS

Many women feel they are not receiving adequate counseling with regard to posttransplant reproductive health. This survey highlights an opportunity to improve both provider education and patient communication to better support women with HT desiring posttransplant pregnancy.

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We conducted a voluntary, confidential, web-based cross-sectional survey of women who were childbearing age (defined as 18-45 years) at the time of HT. Transplants occurred between January 2005 and January 2020. Surveys were conducted across 6 high-volume HT centers in the United States.

RESULTS

There were 64 responses from women who were of childbearing age at the time of HT. Twenty-five women (39.1%) were pregnant before HT, and 6 (9.4%) women reported at least 1 pregnancy post-transplant. Fifty-three percent (n=34) reported they did not receive enough information on post-HT pregnancy before listing for HT, and 26% (n=16) did not discuss their ability to become pregnant with their care team before proceeding with HT. Following HT, 44% (n=28) still felt that they had not received enough information regarding pregnancy. The majority of women (n=49, 77%) had discussed contraception to prevent unplanned pregnancy with their transplant team. Twenty percent (n=13) reported that pregnancy was never safe after transplantation based on the information they had received from their transplant providers.

CONCLUSIONS

Many women feel they are not receiving adequate counseling with regard to posttransplant reproductive health. This survey highlights an opportunity to improve both provider education and patient communication to better support women with HT desiring posttransplant pregnancy.

19. Perinatal depression and risk of maternal cardiovascular disease: a Swedish nationwide study

Abstract

Background and Aims

Increasing evidence suggests that some reproductive factors/hazards are associated with a future risk of cardiovascular disease (CVD) in women. While major (non-perinatal) depression has consistently been associated with CVD, the long-term risk of CVD after perinatal depression (PND) is largely unknown.

Methods

A nationwide population-based matched cohort study involving 55 539 women diagnosed with PND during 2001–14 in Sweden and 545 567 unaffected women individually matched on age and year of conception/delivery was conducted. All women were followed up to 2020.

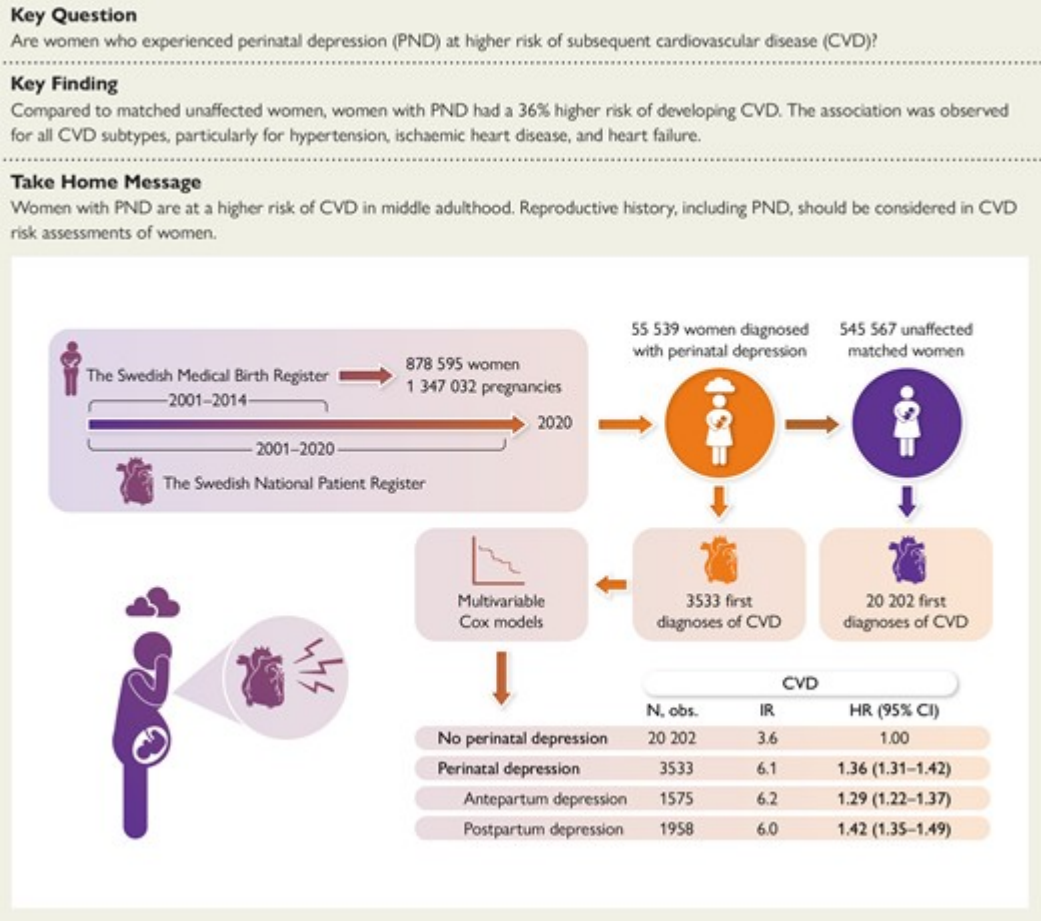
Perinatal depression and CVD were identified from Swedish national health registers. Using multivariable Cox models, hazard ratios (HR) of any and type-specific CVD according to PND were estimated.

Results

The mean age at the PND diagnosis was 30.8 [standard deviation (SD) 5.6] years. During the follow-up of up to 20 years (mean 10.4, SD 3.6), 3533 (6.4%) women with PND (expected number 2077) and 20 202 (3.7%) unaffected women developed CVD. Compared with matched unaffected women, women with PND had a 36% higher risk of developing CVD [adjusted HR = 1.36, 95% confidence interval (CI): 1.31–1.42], while compared with their sisters, women with PND had a 20% higher risk of CVD (adjusted HR = 1.20, 95% CI 1.07–1.34). The results were most pronounced in women without a history of psychiatric disorder (*P* for interaction < .001). The association was observed for all CVD subtypes, with the highest HR in the case of hypertensive disease (HR = 1.50, 95% CI: 1.41–1.60), ischaemic heart disease (HR = 1.37, 95% CI: 1.13–1.65), and heart failure (HR 1.36, 95% CI: 1.06–1.74).

Conclusions

Women with PND are at higher risk of CVD in middle adulthood. Reproductive history, including PND, should be considered in CVD risk assessments of women.



20. Weight Change May Predict Postpartum Readmission Risk in Patients With HDPExtract

Early postpartum weight change is associated with risk for hospital readmission in patients with hypertensive disorders of pregnancy (HDP), as those without weight loss had increased odds of readmission within 8 weeks, according to a study in the *Journal of the American Heart Association*.

Researchers evaluated the relationship between short-term weight change and postpartum hospital readmission in individuals with HDP enrolled in a remote monitoring program, as well as the relationship with admissions related to hypertension or heart failure (HF).

Participants were enrolled from a university medical system from October 2020 to April 2022. They were diagnosed at delivery with HDP (gestational

hypertension, preeclampsia, chronic hypertension, or superimposed preeclampsia).

The exposure was short-term postpartum weight change. Admission weight before delivery was the first weight, and the second weight was the nearest documented within 10 days of delivery. The percentage weight change was grouped into 3 categories: Group 1 included participants with the most weight loss, Group 2 included those with any weight loss less than and including the median percentage weight loss, and Group 3 comprised participants with no weight change or with weight gain.

Self-reported weights in the early postpartum period may serve as a feasible tool for risk stratification among individuals with HDP.

The primary outcome was readmission to a hospital within the university system within 56 days of delivery.

The analysis included 1365 patients with HDP. Group 1 had 683 participants (mean age, 31±5.2 years), Group 2 had 604 participants (mean age, 31±4.7 years), and Group 3 had 78 participants (mean age, 31±5.4 years).

Group 2 lost up to 5.9% of their initial body weight (0.01-19.1 pounds), and Group 1 lost more than 5.9% of their initial body weight (8.0-52.6 pounds).

Participants in Group 3 had an increased rate of hospital readmission within 56 days compared with those in the other 2 groups (14.1% vs 5.8% vs 4.5%, in Group 3 vs Group 2 vs Group 1, respectively; P <.001). No significant difference occurred in the rate of emergency department visits (P =.42).

A comparable pattern occurred in analysis limited to hypertension (11.5% vs 4.3% vs 3.2%, in Group 3 vs Group 2 vs Group 1, respectively; P =.002) or HF (5.1% vs 1.2% vs 0.4%, in Group 3 vs Group 2 vs Group 1, respectively; P <.001) readmissions. Group 3 participants also had increased

diastolic blood pressure (BP) on the day of weight measurement (P =.002) and maximum systolic postpartum BP after weight was recorded (P =.007).

In multivariable logistic regression analysis, Group 3 individuals with no weight loss within 10 days postpartum had greater odds for hospital readmission within 56 days postpartum vs those with the most weight loss (adjusted odds ratio [aOR], 3.9; 95% CI, 1.8-8.6). When limited to readmissions classified as hypertension or HF, a stronger association was observed (aOR, 5.3; 95% CI, 2.2-12.9).

Having no weight loss was associated with greater than 4 times the odds of hospital readmission after adjustment for confounders (aOR, 4.3; 95% CI, 1.5-12.6).

Among several study limitations, weight data were unavailable for every patient, which limited the sample size and potentially introduced selection bias. In addition, variables such as the patients' postpartum diets and activity were not available, and the investigators were unable to identify a weight change threshold with a strong positive predictive value for readmission.

"Self-reported weights in the early postpartum period may serve as a feasible tool for risk stratification among individuals with HDP," the study authors concluded.

21. Long-Term Sex Differences in ASCVD in Individuals With Heterozygous Familial Hypercholesterolaemia

BACKGROUND

Sex differences in atherosclerotic cardiovascular disease (ASCVD) in familial hypercholesterolaemia have been reported but are not fully established. We aimed to assess sex differences in the risk of ASCVD and life-time burden of ASCVD in patients with heterozygous familial hypercholesterolaemia.

METHODS

SAFEHEART is a nationwide, multicentre, long-term prospective cohort study conducted in 25 tertiary care hospitals and one regional hospital in Spain. Participants in the SAFEHEART study aged 18 years or older with genetically confirmed familial hypercholesterolaemia were included in our analysis. Data were obtained between Jan 26, 2004, and Nov 30, 2022. ASCVD and age at onset were documented at enrolment and at follow-up. Our aim was to investigate the differences by sex in the risk and burden of ASCVD in patients with heterozygous familial hypercholesterolaemia, over the study follow-up and over the life course. The SAFEHEART study is registered with ClinicalTrials.gov, NCT02693548.

FINDINGS

Of the 5262 participants in SAFEHEART at the time of analysis, 3506 (1898 [54·1%] female and 1608 [45·9%] male participants) met the inclusion criteria and were included in the current study. Mean age was 46·1 years (SD 15·5) and median follow-up was 10·3 years (IQR 6·4-13·0). Mean on-treatment LDL-cholesterol at follow-up was 3·1 mmol/L (SD 1·4) in females and 3·0 mmol/L (1·5) in males. LDL-cholesterol reductions over time were similar in both sexes (1·39 mmol/L [95% CI 1·30-1·47] absolute reduction in females vs 1·39 mmol/L [1·29-1·48] in males; p=0·98). At enrolment, 130 (6·8%) females and 304 (18·9%) males (p<0·0001) had cardiovascular disease. During follow-up, 134 (7·1%) females and 222 (13·8%) males (p<0·0001) had incident cardiovascular events. Median age at first ASCVD event (mostly due to coronary artery disease) was 61·6 years (IQR 50·0-71·4) in females and 50·6 years (42·0-58·6) in males (p<0·0001). The adjusted hazard ratio for ASCVD in males compared with females during follow-up was 1·90 (95% CI 1·49-2·42) and for cardiovascular death was 1·74 (1·11-2·73). Major adverse cardiovascular disease event (MACE)-free survival from birth was lower in males than females (hazard ratio 3·52 [95% CI 2·98-4·16]; p<0·0001). Median MACE-free survival time was 90·1 years (95% CI 86·5-not estimable) in females and 71·0 years (69·2-74·6) in males. The age at which 25% of female participants have had a MACE event was 74·9 years, this figure was 55·5 years in male participants.

INTERPRETATION

Our findings suggest that the burden and risk of ASCVD are markedly lower in females than males with familial hypercholesterolaemia. The impact of sex needs to be considered to improve risk stratification and personalised management in patients with heterozygous familial hypercholesterolaemia.

22. AF After Cardiac Surgery More Likely in Men, More Deadly in Women

Introduction

Among patients undergoing cardiac surgery, women are less likely than men to develop postoperative atrial fibrillation (AF) after adjustment for other relevant factors, but long-term mortality is higher for those women who do, according to a new analysis.

The findings suggest the need for not only different risk scores for men and women undergoing cardiac surgery, but also, potentially, sex-based care, according to lead author Sergey Karamnov, MD (Brigham and Women's Hospital, Boston, MA).

"We treat females and males the same way," he told TCTMD. "The sizing of the equipment is a little bit different, and the sizing of the valves, . . . but I don't think, anywhere in the country, that any [differentiated] pathways exist to preoperative care, interoperative management, and postoperative management, and long-term follow-up for males and females."

Also, Karamnov said, "historically, a lot of risk scores that we're using in clinical practice right now are derived from studies that have more males than females in their sample size."

Commenting for TCTMD, Catherine Wagner, MD (University of Michigan, Ann Arbor), said the study "highlights how there are all of these different disparities throughout postoperative cardiac surgical care and opportunities

to risk stratify so that we can get patients to have the best outcomes moving forward."

Wagner led a recent study that identified a lower rate of guideline-recommended concomitant procedures to treat existing AF among women compared with men undergoing nonmitral cardiac surgeries.

"Gender differences and women's health is kind of [having] a moment within research, which is really exciting to see," she said. However, because the study looked at long-term morality, which could have several complicating biological and social factors, the findings will remain "hypothesis-generating at this point," she cautioned.

Sex-Based Interaction

For the analysis, published online today in JAMA Network Open, Karamnov and colleagues looked at data from 21,568 patients (mean age 66.5 years; 30.6% women) undergoing cardiac surgery in the Society of Thoracic Surgeons Adult Cardiac Surgery Database between 2002 and 2016. A slightly higher proportion of women compared with men developed postoperative AF (40.8% vs 38.8%), but on multivariable analysis, women had a lower risk than men (OR 0.85; 95% CI 0.79-0.91).

The incidence of postoperative AF increased the risk of death for both men (HR 1.17; 95% CI 1.11-1.25) and women (HR 1.31; 95% CI 1.21-1.42), but more so for the latter group, resulting in a significant interaction between postoperative AF and sex (HR 1.11 for women vs men; 95% CI 1.02-1.23). There was no such gap in mortality risk among men and women who did not develop postoperative AF.

Karamnov argued that the data provide more confirmatory evidence that postoperative AF is not a benign condition, as previously thought. "Postoperative atrial fibrillation is an ominous complication that leads to increased risk of stroke, increased risk of long-term atrial fibrillation, increased need for anticoagulation and subsequent complications of that,"

he said. Given this, when patients develop postoperative AF, especially if they are female, “the follow-up should be more careful [and] home devices have to be utilized more frequently.”

The findings also support further sex-based research into outcomes after cardiac surgery, he said. “[We need] to investigate female patients separately compared to males and not to mix them all up, because I think it actually makes the picture a little bit more murky.”

If risk factors can be identified as key to the disparate mortality in males and females, Karamnov continued, “then we can probably address that on a different level by identifying those females who are at high risk and starting prophylaxis earlier to ensure this complication does not happen.”

Wagner agreed. “As more and more of these gender differences are uncovered, I think people are really understanding that we just need more research in women overall,” she said. “I hope this paper can serve as another call to action for the importance of research stratified by biological sex for outcomes.”

But the findings also have implications for male patients, who are at an increased risk for mortality if they develop postoperative AF, she pointed out.

“One potential driver of the higher mortality for patients with postop A-fib is strokes,” Wagner said, noting that both left atrial appendage ligation and the maze procedure have proven beneficial for stroke prevention in patients with AF. As such, the study “continues to bring awareness of the importance of intervention on A-fib if it's identified preoperatively. But really, this is just the beginning for us to understand how we can truly optimize patient care after cardiac surgery.”

23. **Pregnancy in patients with the Fontan operation**

Introduction

Advances in cardiac surgery and modern medicine enable individuals with a Fontan circulation and single ventricle physiology to enjoy a better quality of life and longer survival. Worldwide estimates are that ~ 70 000 people are living with a Fontan circulation, and approximately half are female with the 30-year survival following Fontan surgery exceeding 80%.1–3

Optimization of care, to improve survival and quality of life for patients with single ventricle physiology, remains one of the great challenges in adult congenital heart disease (ACHD). There is clear scope and need to improve health and quality of life for this expanding patient cohort.

Many women with a Fontan circulation now survive to reach childbearing age and consider whether pregnancy is safe for them and what its impact might be on their well-being and survival. Pregnancy is associated with a reduction in systemic vascular resistance, an increased cardiac output, expansion in blood volume, and an increased risk of thromboembolic disease. These physiological adaptations increase the risk of complications in women with a Fontan circulation who have limited capacity to increase their cardiac output and tolerate the physiological demands of pregnancy and delivery.4

Given the diverse, heterogenous group of patients with a Fontan circulation, research is challenging, and the literature mainly consists of small observational studies with limited follow-up. Legitimate concerns remain regarding the ability of each patient to tolerate the challenges of pregnancy and the uncertainty about any detrimental effects of pregnancy on the long-term prognosis.

Current ESC/AHA guidelines caution that pregnancy in women with a Fontan circulation is associated with increased maternal and foetal morbidity and mortality.5,6 However, the paucity of data limits the ability of care providers to provide accurate pre-pregnancy counselling and evidence-based management plans. A multidisciplinary approach including ACHD cardiologists, high-risk obstetricians, and anaesthetists with expertise in

pregnancy and heart disease is paramount for the best possible maternal and foetal outcomes in this setting.7

We provide a review of the risks of pregnancy in patients with a Fontan circulation, summarize ways to minimize these risks, and provide a comprehensive guide to empower clinicians and in turn their patients. The discussion of pregnancy-related risks should start during the transition age, with a personalized patient approach.

Fontan circulation and how to preserve it

Since 1968, when Francis Fontan reported his eponymous radical palliative procedure, many modifications have been described, mostly with excellent early, mid-term, and longer-term outcomes.3 Today, the most common Fontan operation comprises a total cavopulmonary connection (TCPC) with an extracardiac conduit.2 The pulmonary circulation remains passive as deoxygenated blood flows from the superior and inferior vena cava directly into the pulmonary arteries. This is dependent on low pulmonary vascular resistance and good transpulmonary blood flow, ventricular filling, and cardiac output. The chronically elevated venous pressure and low cardiac output secondary to the absence of a sub-pulmonary ventricle have negative long-term multiorgan effects that impact on pregnant patients.7,8

Multiple studies demonstrate the benefit of routine exercise to improve cardiac output and preserve bone density which may be adversely altered in patients with the Fontan circulation.7,9,10 Maintaining a good posture, healthy diet, and normal body mass index (BMI) have been associated with a better prognosis and with positive psychological outcomes. Maintenance of a healthy weight is especially important in a Fontan circulation where circulation is largely respiratory dependent.7,11 Obesity is associated with significant adverse pregnancy outcomes which include increased rates of gestational diabetes mellitus and hypertensive disorders of pregnancy and foetal complications which include hypoglycaemia, macrosomia, birth trauma, respiratory distress, and neonatal death as well as long-term

implications for both the mother and the offspring.12 Strategies to address elevated body weight should be discussed pre-conception and revisited during pregnancy. Obesity has multiorgan detrimental effects in the Fontan circulation,13 such as sleep apnoea, which is associated with increased pulmonary arterial resistance, a critical factor in the maintenance of a Fontan circulation which may result in deterioration.14 Similarly, in addition to the well-documented adverse effects of smoking during pregnancy (increased rate of miscarriage or ectopic pregnancy, increased foetal congenital malformations, increased risk of placental abruption, placenta praevia, and intrauterine foetal death as well as low birth weight and preterm birth),15 smoking in patients with CHD induces a prothrombotic state, increases oxidative stress, activates the sympathetic nervous system, and impairs endothelial function resulting in further detriment to an already compromised circulation and should be avoided.16 Alcohol exposure during pregnancy is not recommended as alcohol is teratogenic and can impact foetal development during all stages of pregnancy; consequently, guidelines now advise abstinence with the knowledge that there is no safe limit.17 Adverse effects associated with alcohol use in pregnancy include miscarriage, preterm birth, intrauterine growth restriction, and stillbirth,18 and guidance to abstain would be applicable to all pregnant patients, including those with Fontan circulation.

Education of patients, families, general practitioners, cardiologists, and other healthcare providers on the importance of making the right lifestyle choices from childhood is likely to have a significant impact on long-term prognosis and quality of life for these patients.7

Pregnancy counselling and risk stratification

Cardiac assessment for risk stratification

Pre-conception counselling is an essential component of cardiac care for all women with CHD and should be commenced in adolescence prior to transitioning to adult care.19 Women should be encouraged to attend pre-

conception counselling with their partner or a support person. Contraceptive choices should be discussed with all women who wish to avoid pregnancy and be advised to continue during optimization of cardiac status pre-pregnancy. Women with high-risk cardiac conditions where pregnancy is not recommended can be counselled regarding options of adoption and surrogacy.20,21

Women with a Fontan circulation are considered 'high risk' for potential adverse outcomes during pregnancy.1–6 The first goal of pre-conception counselling is to assess the degree of risk to allow an informed patient choice regarding pregnancy. If the patient and her partner decide to proceed with pregnancy, optimizing cardiac status and adjusting medications where necessary, prior to conception, are critically important.

The modified World Health Organization (WHO) risk classification offers an initial risk stratification tool, which can be utilized in combination with the CARPREG I and II scores22,23 and the ZAHARA score24 in patients with complex ACHD.

The modified WHO pregnancy risk classification is based on expert opinion and classifies an 'uncomplicated Fontan' to be category III, meaning that pregnancy confers a significantly increased risk of death and risk of severe morbidity. A 'complicated Fontan' (arterial oxygen saturations <85%, depressed ventricular function, moderate to severe atrioventricular valve regurgitation, refractory arrhythmia, and protein loss enteropathy) is classified as category IV, advising against pregnancy as it is associated with an extremely high risk of maternal mortality or severe morbidity.5 CARPREG I, II, and ZAHARA risk scores are mathematically derived risk scores that use baseline maternal clinical and echocardiographic characteristics to predict maternal complications during pregnancy. The risk scores incorporate factors such as patient history [New York Heart Failure Association (NYHA) functional class, heart failure, or arrhythmia history], physical exam (cyanosis), echocardiographic variables (ventricular function, valve function), and delivery of care (late presentation) into a risk

assessment. For instance, women with Fontan circulation with no history of arrhythmias or heart failure, no ventricular valve dysfunction, no pulmonary hypertension, and who received early antenatal care would have a low-risk score. The scoring systems are not recommended as stand-alone tools but may be utilized in combination with a detailed cardiac history and a systematic clinical evaluation of each case to generate an individualized, patient-centred pregnancy risk assessment for women with a Fontan circulation.

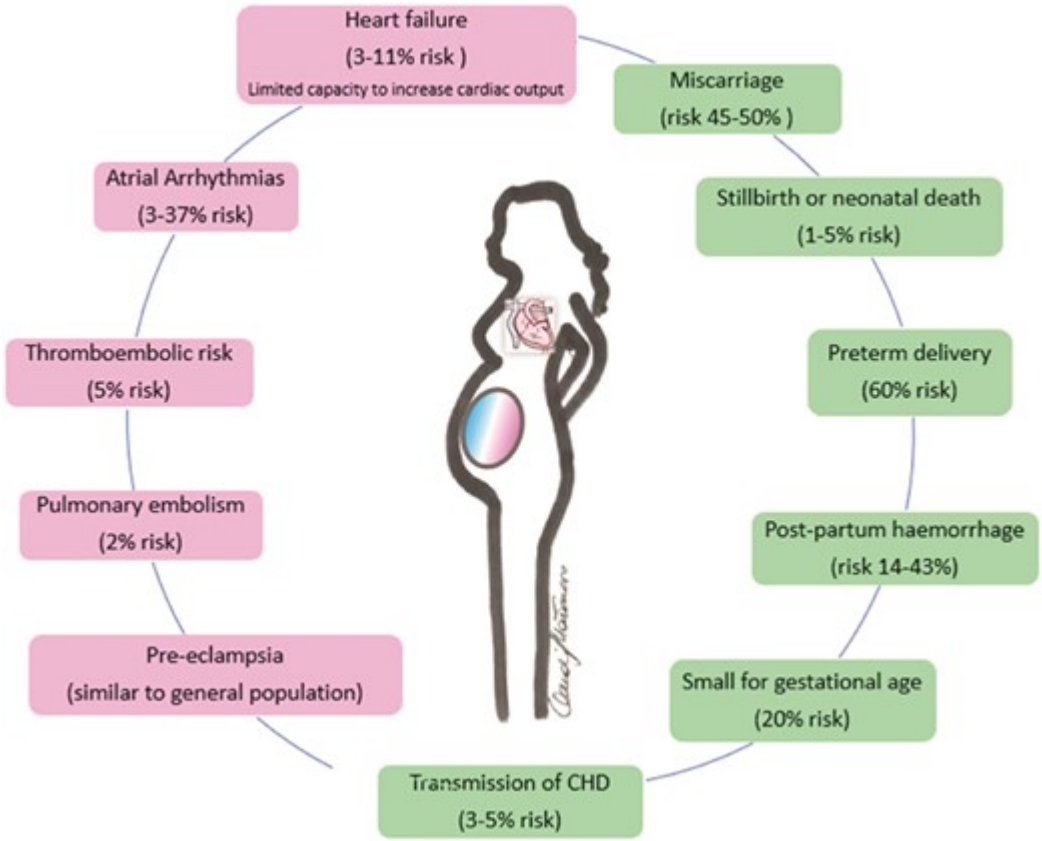
Specifically, a thorough cardiovascular examination looking for evidence of elevated JVP, cyanosis, chest deformities, and any evidence of Fontan obstruction, even mild, or valve regurgitation is paramount. Cardiac imaging with transthoracic echocardiography and cardiac magnetic resonance imaging (MRI) as a baseline prior to pregnancy are complementary and need to be recent (echocardiogram within 6 months, cardiac MRI within 12–24 months). Identification of any obstruction in the circulation should prompt right heart catheterization and Fontan intervention as appropriate, including stent conduit implantation if required. Optimal Fontan flow facilitates transpulmonary flow and cardiac output, and thus, we speculate better placental perfusion and foetal somatic growth. Patients are at risk for both diastolic and systolic dysfunction. Systemic ventricular dysfunction is associated with worse prognosis during and after pregnancy. In cases of borderline ventricular systolic dysfunction, stress echocardiography may be useful to assess contractile reserve. Blood tests including brain natriuretic peptide (BNP), biochemistry, liver and kidney function tests, iron status, and thyroid profile should be incorporated into the risk assessment with caution that BNP is less useful in the setting of atriopulmonary connection (APC) and atrioventricular connection (AVC) where it may be elevated in the setting of normal functioning ventricular physiology. The diagnostic utility of BNP in the Fontan circulation lies mainly in the TCPC.25 Functional status assessed by cardiopulmonary exercise testing provides a surrogate for cardiac output and provides information on oxygen saturation, blood pressure, and chronotropic competence.26 A recent ultrasound scan of the

liver and spleen (within 24 months) and liver markers are also useful in every patient with a Fontan circulation to assess for Fontan-associated liver disease (FALD). The aim is to exclude portal hypertension which would be suggested by thrombocytopenia, ascites, splenomegaly, collateral circulation on imaging, or elevated hepatic venous pressure gradient. Portal hypertension and cirrhosis are common long-term complications of a Fontan circulation associated with a poor prognosis. Patients with liver cirrhosis, distinct from those with FALD, have a high risk of miscarriage, prematurity, and perinatal death.27 Further, during pregnancy, compressing the IVC can aggravate portal pressures and liver congestion.

Medications taken by the patient are reviewed in the context of pregnancy for teratogenic effects. Renin angiotensin aldosterone system (RAAS) inhibitors and mineralocorticoid receptor antagonists are contraindicated due to well-documented foetal anomalies.28,29 Beta-blockers should be continued during pregnancy if indicated with additional foetal growth scans at 4 weekly intervals because of the risk of potential low birth weight.30 Diuretic use is not advised unless there is decompensation, where it should be used with caution because of a reduction of pre-load.1

Counselling of possible complications

Cardiac arrhythmias, heart failure, thromboembolism, and haemorrhage are the most frequently encountered maternal complications during pregnancy in women with a Fontan circulation.1 Patients should be counselled that observational data demonstrate 3–37% risk of heart arrhythmia, 5% risk of thrombosis, and 3–11% risk of heart failure (*Figure 1* and *Table 1*).1,28,31–36



Cardiovascular and obstetric complications during pregnancy in patients with Fontan circulation

Study	**A systematic review**	**A retrospective study**	**Nationwide inpatient sample**
	PubMed and Cochrane Library	**ACHD centres in the UK**	**Hospitalizations in the USA**
	Years 1990–2017	**Years 2005–16**	**Years 2000–18**
Authors/year of publication	Garcia Ropero *et al.*1/2018	Cauldwell *et al.*31/2018	Sobhani *et al.*32/2023
Type of Fontan	Atriopulmonary 54	Atriopulmonary 13	NA
	Right atrial–	Lateral tunnel	

Study	A systematic review	A retrospective study	Nationwide inpatient sample
	PubMed and Cochrane Library	ACHD centres in the UK	Hospitalizations in the USA
	Years 1990–2017	Years 2005–16	Years 2000–18
	atrioventricular connection 11	18	
	Total cavopulmonary connection 53	Extracardiac 17	
	Other 3	Other 2	
Number of pregnancies	255	124	509
Cardiovascular complications (% of total pregnancies)			
Heart failure	3–11% (prevalence 3.9%)	13.2%	CSMM 5% (vs. 0%)a
Pulmonary embolism	2%	1.9%	
Arrhythmias	3–37% (prevalence 8.4%)	11.3%	
Stroke	2%	—	
Obstetric complications (% of total pregnancies)			
Miscarriage	45–50%	54%	Not reported

Study	**A systematic review**	**A retrospective study**	**Nationwide inpatient sample**
	PubMed and Cochrane Library	**ACHD centres in the UK**	**Hospitalizations in the USA**
	Years 1990–2017	**Years 2005–16**	**Years 2000–18**
			54%
Preterm delivery	60%	72% (44%—SPD, 20%—PPROM)	16% (vs. 7%)a
Antepartum bleeding	—	Not reported	5% (vs. 1%)a
Hypertensive disorders of pregnancy	—	3.8%	14% (vs. 8%)a
Small for gestational age (SGA)	20%	55.6% (SGA ≤10th centile)	Not reported
Neonatal death and stillbirth	1–5%	3.2%	Not reported
Post-partum haemorrhage	14%	43%	13% (vs. 3%)a
Risk of transmission	3–5%	Not reported	Not reported

Study	A systematic review	A retrospective study	Nationwide inpatient sample
	PubMed and Cochrane Library	ACHD centres in the UK	Hospitalizations in the USA
	Years 1990–2017	Years 2005–16	Years 2000–18
of heart disease			

aValues in brackets indicate percentages in women without Fontan circulation.

Obstetric complications such as preterm rupture of membranes, preterm delivery (26–34 weeks), and post-partum haemorrhage (PPH) are relatively common among women with Fontan circulation (*Table 1*).1,31–34 Complications such as pregnancy-induced hypertension and pre-eclampsia are not more frequent in women with ACHD compared to the general population.35 The foetus is at risk of miscarriage, foetal growth restriction, and prematurity, particularly if the mother is cyanotic. Studies have reported 45–50% risk of miscarriage, 60% risk of preterm delivery (data include spontaneous and iatrogenic preterm deliveries), 20% risk of small for gestational age, and 1–5% risk of stillbirth or neonatal death.1,31–34

There is also an increased rate of infertility which is likely multifactorial and a combination of chronic disease, hypoxia, and clotting abnormalities and should also be discussed during pre-conception counselling.7 There are increased rates of amenorrhoea and early miscarriage particularly in women with low cardiac output and/or cyanosis.36–39 In our practice, women with a regular cycle who do not conceive within 12 months of unprotected sexual intercourse are referred to reproductive medicine specialists for further investigations. Decisions regarding the safety of assisted reproduction technologies are complex and patient dependent. Ovulation stimulation

and *in vitro* fertilization are reported in a small number of women with Fontan circulation.38 Modified hormonal stimulation protocols and single-embryo transfer can be considered to minimize risk of haemodynamic instability or multiple pregnancies, respectively.39

Anticoagulation management

Patients with a Fontan circulation have an increased risk of thromboembolism secondary to the turbulence and stasis associated with the complex circulation.1,3,31,33,39 Thromboembolism may occur in the pulmonary or the systemic circulation.39 The prothrombotic effect of pregnancy increases the risk of thromboembolism significantly; consequently, our practice is to advise all patients with Fontan circulation to take aspirin 150 mg daily until 36 weeks gestation in addition to prophylactic low molecular weight heparin (LMWH) until 6–12 weeks following delivery. In patients with a higher risk of thrombosis [previous thrombosis, atriopulmonary (AP) Fontan, systemic ventricular dysfunction, fenestration, spontaneous echo contrast on echocardiography, Fontan obstruction, or atrial arrhythmia], we recommend therapeutic LMWH instead of prophylactic in addition to aspirin. Decisions regarding anticoagulation in patients without the above additional risk factors are controversial and differ between experts.28,31,33,34,39 Anticoagulation needs to be considered on an individualized, patient-centred basis as the risk of bleeding in pregnant patients with Fontan circulation is also elevated. In selected cases, where warfarin is indicated, it can be introduced after the first trimester (because of increased rates of miscarriage and embryopathy)28 with LMWH used as the alternative in the first trimester and restarted 2–4 weeks before delivery when warfarin would be ceased.1,33,34,39

General and social advice

General advice includes folic acid supplementation from 3 months pre-conception to 12 weeks gestation; up-to-date vaccinations (COVID

vaccination40 and pertussis vaccine after 16 weeks gestation); cervical cancer surveillance preconception; and to schedule pending operations or procedures prior to conceiving.

Patients with ACHD have an increased risk of congenital heart disease in their offspring, ~ 3–50% in cardiac conditions.29,41 A foetal echocardiogram is recommended at 19–22 weeks gestation to assess for foetal congenital cardiac conditions.7,29,33

The financial and social aspects of pregnancy for a patient with Fontan circulation can be challenging. There may be difficulty maintaining regular employment. There can also be geographical challenges associated with attendance at tertiary clinics.

It is paramount to discuss with the patient the lack of data on the potential long-term adverse effect of pregnancy on the heart in women with Fontan circulation.4,28,29,39,42 The potential implications of this for the patient in the future and for her family should be considered.

Contraception

The combined oral contraceptive pill (COCP; with oestrogen and progesterone) is associated with risks of thromboembolic complications and hypertension43,44 and has traditionally been considered contraindicated, although many patients are still prescribed this form of contraception.19 Potentially, some of the risk may be mitigated in patients who are on concomitant therapeutic anticoagulation,7 and the risk of the COCP should be considered balanced against the risk of pregnancy.28 Progesterone-only pills are safe and effective especially high-dose desogestrel which inhibits ovulation.5 Long-acting reversible contraceptives like levonorgestrel-containing intrauterine contraceptive device (LNG IUCD) or implants (Nexplanon) are considered safe and effective.5,19,28 Ideally, women with Fontan circulation should have a LNG IUD inserted as a day-case procedure in a tertiary setting due to risks of vasovagal episodes during cervical manipulation.5,28

Tubal ligation (sterilization) or vasectomy should be discussed in women with modified WHO class IV where pregnancy is contraindicated or not desired.5,19,29

Pregnancy

Pregnant patients with Fontan circulation should be managed by a multidisciplinary team (MDT) 'pregnancy heart team' in a high-risk cardio-obstetric clinic with input from obstetricians, ACHD cardiologists with expertise in pregnancy, maternal foetal medicine specialists, anaesthetists, cardiac nurse specialist, and midwives.4–7,19,32–36,42–44

Close follow-up of pregnant women with a Fontan circulation is required to identify deterioration or complications at an early stage. The consensus is that patients should be reviewed monthly at a minimum during pregnancy, often more frequently as the pregnancy progresses or if clinical deterioration occurs.5,39 Transthoracic echocardiogram should be performed at least each trimester dependant on clinical status.33

At each clinic visit, a thorough clinical history followed by detailed cardiovascular examination including auscultation, oxygen saturation, heart rate, and blood pressure is recommended.33 Medications are reviewed, and patient concerns are addressed. An obstetric examination follows at each visit including a urinalysis and foetal growth scans every 4 weeks from 24 weeks gestation.

Advanced cardiac imaging such as non-contrast cardiac MRI is carried out when there is a strong clinical indication. Gadolinium contrast is avoided due to concerns in animal models regarding potential rheumatological, inflammatory, or infiltrative skin conditions in the infant and an increased risk of perinatal death45; however, this potential risk of harm must be balanced against the need for the investigation on a case-by-case basis.

Termination of a pregnancy

If the pregnancy is unplanned or the patient is classified as mWHO class IV, termination of pregnancy (TOP) should be discussed.5,6 Similarly, if during pregnancy there is a significant deterioration in clinical state, TOP should be considered. If there is clinical deterioration at any stage, hospital admission and obstetric and cardiac counselling should be readily available.5

Termination of pregnancy can be achieved medically, with a combination of mifepristone and misoprostol, or surgically.5 In the context of Fontan circulation, in the absence of comparative data, expert opinions differ on the safety of medical vs. surgical management. The risk and benefits of each option must be judged on an individual basis considering the gestation. All medical terminations, after the misoprostol has been administered, should be performed as an inpatient to allow close monitoring as misoprostol can cause hypotension and heavy bleeding may occur at any stage. Surgical TOP should be performed in a tertiary unit with the support of a pregnancy heart MDT. Antibiotics are recommended by most gynaecologists during surgical TOP to prevent endometritis which occurs in 11–22% cases post-abortion.5 Prostaglandin F (PGF) compounds should be avoided as they can increase the pulmonary artery pressure and decrease coronary perfusion.5

Delivery

Delivery should occur in a tertiary centre with an experienced cardio-obstetric team as is the case for all moderate- and high-risk pregnancies.4–6,28,33 A delivery plan should be in place between 28 and 32 weeks gestation and be distributed and then discussed regularly.5,28,33,46

Elective vaginal delivery with early epidural anaesthesia is preferred in most cases, and it is associated with reduced risk of infection, thrombosis, and blood loss.5,28,47 Caesarean delivery is recommended for obstetric indications or for women with Fontan circulation in heart failure.1,7,28,31 Delivery is recommended between 37 and 39 weeks. For women having a vaginal delivery, an assisted second stage is often advised.5,28,33,47 Depending on the level of compromised heart function, a

period of active pushing may be possible, but the duration should be judged on a case-by-case basis.

Continuous cardiotocography (CTG) is recommended in labour.5 Maternal blood pressure, heart rate, oxygen saturation, and continuous electrocardiogram (ECG) monitoring are indicated, and an arterial line may be considered in high-risk patients.5,32 Strict fluid balance is recommended during labour. Adequate hydration helps maintain central venous pressure and blood flow through the cavopulmonary connection to the lungs.47 Immediately post-delivery, autotransfusion of blood from the placenta into the maternal circulation may cause a transient volume overload and contribute to cardiac decompensation; therefore, this needs to be monitored and small doses of diuretic may be considered.

Due to the risk of PPH, adequate intravenous (i.v.) access, cross-matched blood, and active management of the third stage of labour are advised and help reduce blood loss.48 A slow and cautious i.v. infusion of oxytocin reduces the risk of PPH and is preferred to avoid risks of hypotension and vasodilatation associated with bolus oxytocin administration,5 which in turn can have devastating consequences in women with a single ventricle. Prostaglandin PGE1 (misoprostol) is considered safe for treatment of PPH whereas ergometrine and PGF analogues should be avoided.33 Fluid management should be handled with care,33 and adequate fluid resuscitation is recommended in the event of major PPH as patients with Fontan circulation are highly preload dependant.

Infective endocarditis prophylaxis is not recommended routinely for spontaneous vaginal delivery according to the ESC/AHA guidelines5; it should be considered for general ACHD indications29 and in patients with a palliated single ventricle, especially if cyanotic.

For Caesarean section, the use of low-dose epidural anaesthesia or sequential low-dose combined spinal–epidural is preferred over general anaesthesia. The negative intrathoracic pressure created from spontaneous

ventilation improves blood flow to the lungs and oxygenation. Supplemental oxygen further reduces pulmonary vascular resistance. If general anaesthesia is needed, the left lateral decubitus position is crucial to maintain preload with single ventricle physiology. Ventilator parameters should keep airway pressures low to aid oxygenation.5,39,44,47

Management of Fontan complications during pregnancy

The most common complications during pregnancy are maternal arrhythmias, thromboembolism, and heart failure.1,4,28,31–34,36,42

New-onset persistent palpitations should be investigated with an ECG and ambulatory electrocardiographic monitoring to evaluate for tachyarrhythmias and assess symptom–rhythm correlation. The increase in circulating blood volume in normal pregnancy may result in atrial distension which may trigger atrial tachyarrhythmias with potential haemodynamic disturbances. Supraventricular arrhythmias are common in pregnancy whereas ventricular arrhythmias are rare.1 Beta-blockers or antiarrhythmic drugs such as flecainide (maternal and foetal QT intervals and foetal heart rate should be monitored) can be used.49 Synchronized electrical direct current cardioversion (DCCV) is safe and effective and should be considered in persistent arrhythmia unresponsive to pharmacotherapy or as first-line when arrhythmia is associated with haemodynamic instability. In the case of maternal haemodynamic instability, adult resuscitation algorithms should be adhered to without delay or concern for potential harm to the foetus. In less emergent situations where foetal viability is established, foetal CTG is recommended during maternal DCCV. Anticoagulation with LMWH is recommended, if not already established, in cases of atrial fibrillation or flutter.49

Symptoms or signs of heart failure should be investigated with a BNP and a transthoracic echocardiogram. A normal BNP is helpful in excluding heart failure during pregnancy.50,51 Symptoms of increasing fatigue, reduced exercise tolerance, and functional decline with increasing NYHA class

should raise suspicion of impaired ventricular function and a failing Fontan. These symptoms can be difficult to differentiate from normal pregnancy physiology, particularly in the third trimester, when shortness of breath, ankle swelling, and fatigue are common. Diuretic therapy should be used with caution in the presence of fluid overload or evidence of cardiac failure. Acute heart failure with any degree of haemodynamic instability in pregnancy should trigger admission to hospital with consideration of an earlier delivery particularly when the patient remains compromised despite optimal heart failure therapy. The priority is always to adequately treat the mother as her cardiac instability poses the biggest threat to the foetus. Premature delivery may be necessary on occasion.

Thromboembolic risk is reduced by appropriate thromboprophylaxis, and for those on therapeutic LMWH for indications such as mechanical valves, strict monitoring of anti-Xa levels is recommended.5,28 If pregnancy is complicated by pulmonary embolism with haemodynamic compromise, thrombolysis should be considered.52 Surgical embolectomy, catheter-guided thrombectomy, and extracorporeal membrane oxygenation (ECMO) are alternatives that may be considered depending on local expertise in the less common instances where systemic i.v. thrombolysis is contraindicated.53

Post-pregnancy

Post-pregnancy care

Following an uncomplicated delivery, a period of 24 h of close observation and continuous cardiac monitoring within the delivery unit or on the obstetric high dependency unit (HDU) is advised prior to transfer to the postpartum ward.33 There should be a low threshold for transfer to the intensive care unit (ICU) for 24–48 h following delivery, particularly where there are complications during delivery or concern for cardiac decompensation. Patients should expect to remain in hospital for a minimum of 72 h for uncomplicated deliveries prior to discharge to monitor

for any complications in the immediate postpartum period.33 Outpatient follow-up with an ACHD cardiologist and an obstetrician should be arranged within the first 6 weeks post-delivery.32

The risk of venous thromboembolism (VTE) is highest during the postpartum period rising to 15–35-fold.7 Prophylaxis with LMWH and compression stockings are recommended for up to 6 weeks unless there is a significantly elevated bleeding risk.

General considerations

Discussion about contraception and avoidance of a new pregnancy within a minimum period of 18 months to allow re-assessment of risks after complete vascular remodelling is paramount.54

Breastfeeding is supported but increases the maternal haemodynamic load, which is potentially problematic in patients with underlying cardiac disease with impaired ventricular function. Medication safety during breast feeding should be reviewed.

All women should be screened for postnatal depression. Additional social and psychological support may be needed, particularly for women who have suffered from pregnancy loss or have experienced deteriorating maternal health during pregnancy.

Further discussion about lifestyle changes is crucial. Exercise is important moving forward to reduce the risk of cardiovascular events and for the well-documented psychological benefits. Women are encouraged to optimize weight and to be physically fit, in keeping with our aspirational mantra of 'fit and athletic' for optimal health in the long term.19,54

Future considerations

Future studies should address the impact of pregnancy and multiple pregnancies on the long-term morbidity and survival of patients with Fontan circulation. This is the main area of the current literature where data are

lacking. Multicentre collaborations may be necessary to facilitate meaningful results to inform clinical practice and patient guidance.

Discussion

Well-selected and optimized patients with Fontan circulation can have successful pregnancy. The pregnancy is not free from risks, and a patient-centred and holistic and systematic approach (*Table 2*) encompassing pregnancy care by a highly experienced MDT is essential for good outcomes. Patients should be explained and empowered about the maternal and foetal risks already during the transition age, with a tailored approach to the topic also explaining the need for investigations to risk stratify their pregnancy-related risk.

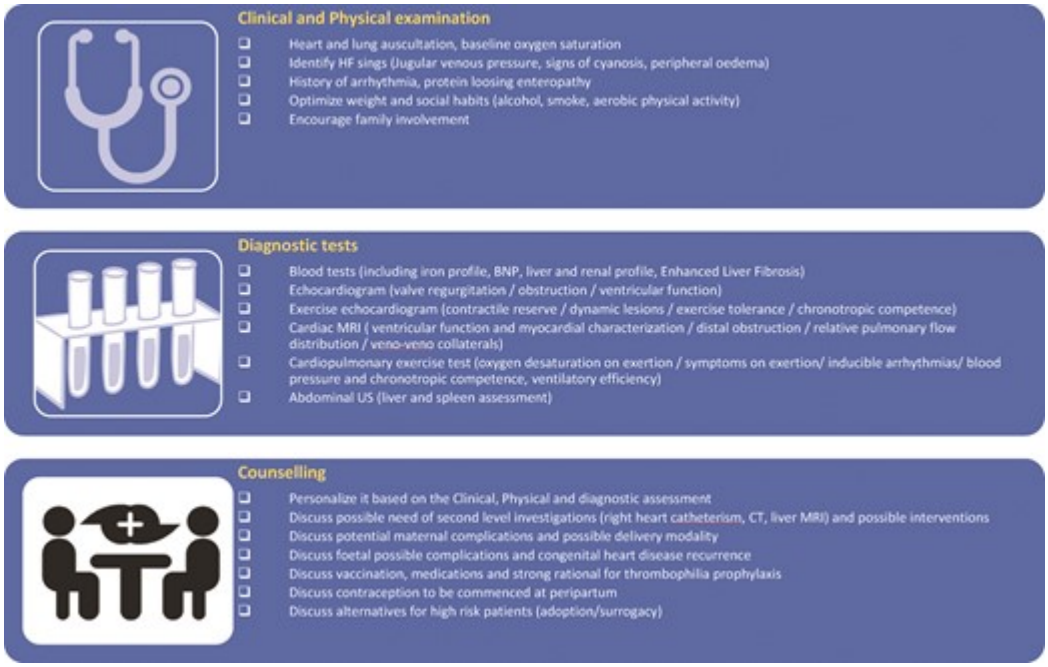


Table 2

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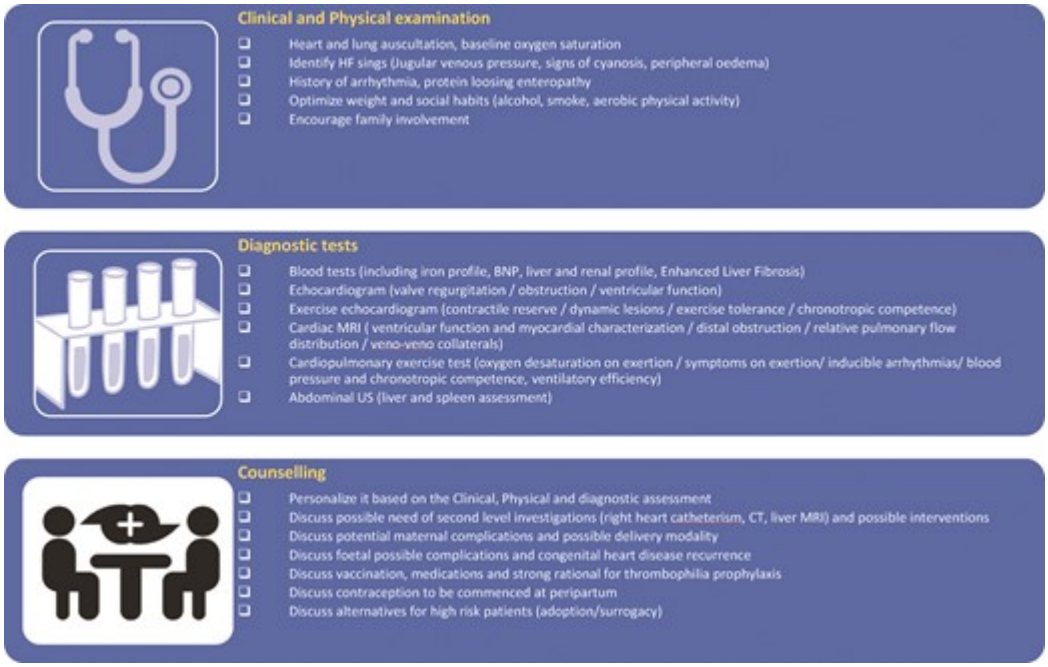
The checklist to counsel patients with a Fontan circulation



Data regarding the long-term implications of pregnancy in women with Fontan circulation are sparse.7 This makes counselling regarding the impact of pregnancy in the long term challenging. In a systematic review, examining 6 studies: 255 pregnancies in 133 women with Fontan circulation, there were 115 live births and no maternal deaths.1 Although these observational data do not reflect the full spectrum of patients with Fontan circulation, but rather a selected and optimized group, it does offer some reassurance that in cohorts of stable women with a well-functioning Fontan circulation, pregnancy outcomes do not seem to be associated with mortality. In a study analysing the outcomes of 45 pregnancies in 30 women with Fontan circulation from the Australia and New Zealand Fontan Registry, there was a trend towards increased detection of thrombus and thromboembolic events in patients with pregnancy vs. patients without pregnancy; however, this difference did not achieve statistical significance when age and type of Fontan circulation were considered in the propensity score analysis.42

Conclusions

Adopting a proactive approach is critical to the care of patients with Fontan circulation during pregnancy. This should include education from their early years on the merits of maintaining an optimal weight and physical fitness. These choices will have a positive impact on a patient's health regarding pregnancy and beyond, improving both quality of life and longevity. It is essential that guidance on family planning, including contraception, is given early, ideally before transition to adult care, in addition to discussions regarding the risks associated with pregnancy and revisited regularly thereafter. Tertiary centre, multidisciplinary care, and frequent clinical review during pregnancy allow for early identification and management of potential complications. Women with an uncomplicated Fontan circulation should be reassured that it is possible to have an uncomplicated pregnancy if they are cared for by an expert MDT in a tertiary environment.

24. A forward-looking approach in women living with the Fontan circulation: from cardio-obstetric to cardio-reproductive medicine

Cardiovascular diseases (CVD) represent the leading cause of pregnancy-related mortality in higher-income countries, and the increased number of women with congenital heart diseases (CHD) surviving up to reproductive events seems to contribute to the excess maternal mortality rate in this setting.1 However, novel surgical procedures, including the Fontan operation,2 have been truly a 'game-changer' enabling reproductive planning. Being pregnant represents a stress test for any woman. Successful adaptation to the new requirements of the pregnant state has the aim to maintain a balance between foetal development and maternal health through substantial haemodynamic and metabolic changes.3 In women with Fontan circulation and single ventricle physiology, the chronically elevated venous blood pressure and limited capacity to increase cardiac output pose several challenges to adaptive phenomena of the foetal–maternal unit. Recurrent miscarriage, low birth weight, and preterm birth have been consistently reported as adverse effects of Fontan circulation on pregnancy, with placental insufficiency being speculated as the possible pathophysiological clue.4 Also, atrial arrhythmia, left ventricle dysfunction,

and thrombo-embolic events represent major risks for maternal health in women with Fontan circulation during pregnancy and in the post-partum.5 That being so, the World Health Organization (WHO) suggests caution in reproductive counselling with women after Fontan operation; they are included in high risk (when the operation in uncomplicated) or very high risk categories (in case of complications, including reduced oxygen saturation, depressed ventricular function, moderate to severe atrioventricular regurgitation, refractory arrhythmias, and protein loss enteropathy). However, an individualized evidence-based counselling is required to empower these women to make informed choice about their reproductive health. Montanaro *et al.*2 cover the reproductive challenges in women with Fontan circulation and, in doing so, rise important issues that can be translated also to other CVD that ensue early in a woman's life.

The first point that emerges very clearly is that the foundations for a successful pregnancy should be laid as early as transition through puberty occurs. The discussion about reproductive health in adolescents with the Fontan circulation should not be limited to contraceptive counselling, which is still mandatory and should explore the whole set of possibilities that provide the best benefit–risk ratio. Indeed, individuals experiencing diseases early in life, among which congenital anomalies have one of the strongest impact, are more likely to remain childless across their lifespan. In recently published data from a Danish cohort, individuals with CHD, despite a similar prevalence of infertility compared to healthy controls, were more likely to remain childless.6 The prevalence of voluntarily childless has not been specifically assessed in women with Fontan circulation, but fears around the impact of pregnancy on the altered cardiovascular physiology and vice versa, together with concerns to transmit heart disease to the offspring, may represent reasons to avoid pregnancy. That being so, a balanced narrative of the impact of Fontan circulation on future chance of motherhood should be offered to every woman taking into account individual characteristics and emphasizing the role of a healthy life-style (physical exercise, maintenance of normal body weight, avoidance of

smoking) early in the life course trajectory to improve long-term general and reproductive health. As maternal age increases in the general population, counselling about the impact of age on fertility and pregnancy outcome is essential in young women and even more in those with Fontan circulation, in order to optimize fulfilment of their reproductive goals.

Based on Montanaro *et al.*,2 a multidisciplinary approach should be dedicated to women with Fontan circulation before, during, and after pregnancy; the model of 'cardio-obstetrics' proposed few years ago finds its highest application in high-risk patients such as these women.1 However, there is still a gap in specific training and education both in cardiologists and even more in other specialists, including obstetrics, gynaecologist, anaesthesiologists, and primary care physicians, who may be involved in care of these women in different moments along reproductive lifespan. Although an effort of Scientific Societies to define guidelines for management of pregnancy in women with CVD, evidence-based recommendations for management of pregnancy after Fontan operation come from expert opinion and observational data in relatively small number of patients.1,7 Therefore, these patients need to be cared of in tertiary centres by highly specialized team in cardio-obstetrics, but variable availability of resources across different regions may result in inequalities, potentially affecting foetal–maternal outcomes.

Finally, an important knowledge gap emerges in the long-term effects of pregnancy on cardiovascular prognosis of women with Fontan circulation.2 Adverse pregnancy outcomes, including preterm delivery and low birth weight/intrauterine growth restrictions, which are the commonest late obstetric complications in Fontan women, have been associated with increased risk of cardiovascular events later in life.3 It has still to be defined whether the excess risk is due to the underlying cardiovascular susceptibility unmasked by pregnancy-induced stress on cardiovascular system, or factors related to pregnancy itself may cause a derangement in mechanical, inflammatory, or metabolic homoeostasis modulating the future cardiovascular risk.3 There are no data supporting counselling about the

long-term impact of a complicated, or even uncomplicated, pregnancy on arrhythmias rate, ventricular dysfunction, heart transplant rate, and mortality in these patients, because the post-delivery follow-up in published studies is limited, with the longest covering a median of 3.6 years (range 1.2–7.5 years).8 As life expectancy in women with Fontan circulation has increased over time, owing to better patient selections and improvement of surgical techniques,9 some of these women will also face another major challenge to their cardiovascular and metabolic health, as they will transit through menopause. It has even been suggested that early follicular depletion could be encountered in women with Fontan circulation, who showed lower levels of antimullerian hormone (AMH), a marker of ovarian reserve, possibly because ovarian tissue is highly susceptible to low blood oxygenation and slight changes in perfusion.10 That being so, more research will be needed as the population of operated women ages and navigates menopausal transition, in order to explore the effects of oestrogen deprivation, that is known to affect cardiometabolic health at several levels (atherogenic changes in lipid profile, insulin resistance, endothelial dysfunction, vascular remodelling, increased sympathetic tone).11

In conclusion, pregnancy is a challenge to the health of women with Fontan circulation and their infants; a successful management depends upon a long journey that starts during adolescence and may have implications on future health, especially after menopause. That being so, the interdisciplinary contamination highly auspicated with the introduction of the model of cardio-obstetric medicine should be expanded before and beyond pregnancy, along the reproductive *fil rouge* that modulates cardiovascular health in any woman, but even more so in this high-risk population. As survival has substantially increased during last decades, cardio-reproductive medicine should be a priority in the care of women with Fontan circulation, in order to support informed choices around motherhood, minimizing risks and discriminations at once.

25. Phenol, Paraben Exposure Linked to Hypertension During Pregnancy

Phenol and paraben exposure may be associated with hypertension during pregnancy, according to a study published online Aug. 14 in Environmental Health Perspectives.

Julia R. Varshavsky, M.P.H., Ph.D., from the Bouvé College of Health Sciences at Northeastern University in Boston, and colleagues examined associations between individual phenols, parabens, and their mixture on maternal blood pressure (BP) measurements and hypertension during pregnancy among 1,433 women. The relationships were examined cross-sectionally at two time points during pregnancy (16 to 20 and 24 to 28 weeks of gestation) and longitudinally.

The researchers found that exposure to multiple analytes and the overall mixture was associated with a trend toward higher odds of hypertension during pregnancy, especially at 24 to 28 weeks of gestation (adjusted mixture odds ratio, 1.57). Individual analytes were also associated with lower systolic BP (SBP) and higher diastolic BP (DBP), with the results from the linear mixed models most consistent for methyl paraben or propyl paraben with increased DBP (β = 0.78 and 0.85, respectively), and for bisphenol A, which was associated with lower SBP (β = −0.57). There was evidence of effect modification by fetal sex, with a strong inverse association between overall exposure mixture and SBP among those carrying female fetuses.

"These everyday products that we think are safe may be actually harming us and our babies at a critical time during pregnancy," Varshavsky said in a statement. "In the largest study to date, we found that the combined effect of phenol and paraben mixtures increased risk of hypertension during pregnancy among a vulnerable population of women in Puerto Rico who are also dealing with a disproportionate burden of exposure to other toxic chemicals, poverty, and climate change-related disasters like hurricanes and flooding."

26. Beyond Parental Leave: Addressing Infertility, Pregnancy, and Postpartum Complications Among Cardiologists

Introduction

Cardiologists experience a disproportionately greater risk of complications on the road to parenthood as compared to their nonphysician counterparts. For many, difficulties begin with infertility, which is experienced at a reported rate of 1 in 4 surveyed physicians.**1** A recent *JACC* paper reported about 38% of female cardiologists also experienced pregnancy complications, a rate nearly double that of their nonphysician counterparts.**2** Issues including infertility and pregnancy complications are amplified among physician trainees, as training years often parallel periods of life in which individuals and/or their partners contemplate parenthood. As such, the focus on complications around parenthood as well as the search for effective support mechanisms is paramount.

Unique to physicians, young adult life is often filled with physical, emotional, and financial strains, including long working hours, complex tasks in the hospital, interrupted sleep, extended training into the late 30s, and the specter of repayment of significant education debt. Many of these aspects of training and early career practice may underscore the disproportionate rates of complications surrounding planning for parenthood among cardiologists and cardiology-trainees.

A recent focused session on this topic at the 2024 American College of Cardiology Annual Scientific Sessions highlighted programmatic and policy changes enacted at academic centers throughout the country that addressed challenges surrounding achieving parenthood (**Figure 1**). We highlight approaches undertaken by national physician organizations and the authors of this paper with their respective institutions from this session and from other sources. We also outline future focus areas for change.

Implemented Policies and Programs Toward Addressing Parenthood Complications

Policies and programs as well as future directions targeting infertility, complication support networks, and lactation. AMWA = American Women's Medical Association.

Implemented programs and policies

Infertility summit/coverage at work toolkit

National multispecialty organizations, including the American Women's Medical Association (AMWA) have spearheaded efforts toward actionable change to address infertility.**3** Their 5-part strategic approach includes:

1. to increase fertility awareness starting with early education in college and continuing through medical training,
2. to target both insurance coverage and access to fertility assessment and care among all physicians,
3. to ensure support systems among physicians that can provide both emotional support and wisdom during the fertility treatment journey,
4. to focus research highlighting the economic benefits of supporting fertility treatment among the physician workforce,
5. and to enact supportive policy from state to a national level.**1**,**3**

In partnership with RESOLVE, a national infertility association, AMWA organized annual physician infertility summits spanning 2021 to 2023 to accomplish these aims. One of their most actionable items features a "Coverage at Work" toolkit. This toolkit includes documents like letter templates for physicians to advocate for infertility coverage at their organizations at multiple levels, from human resources to institutional leadership. Their toolkit also includes infertility insurance coverage facts and resources. All seminar lectures and toolkits are readily downloadable from their website.**3**

Infertility, pregnancy, and postpartum complications support network

One of AMWA and RESOLVE's strategic approaches is to ensure support systems for physicians provide emotional backing and wisdom regarding reproductive life events. Responsive to this, the University of Pittsburgh has created a support network for physician and physician-trainees to provide support and information about topics from infertility through postpartum complications.

To "construct a village" of support, a committee, including multispecialty program directors, convened a leadership team who were both impacted on a personal level and/or were passionate about supporting physicians who had experienced difficulties around reproductive issues. They constructed a 10-question/5-minute survey that was inclusive, short, and anonymous. Embedded in the survey were requests for personal recommendations on resources including supportive groups, mental health professionals, physicians, doulas, and faculty peers that they had found useful. From this, a list of local resources was created. The survey also sought to obtain qualitative information with open-ended questions including "what other topics can you provide support for" and "how else can we best support you?" A total of 11 support topics were identified: infertility, high-risk pregnancy, multigestational pregnancy, miscarriage, late pregnancy loss, neonatal illness, adoption, postpartum anxiety and/or depression, unplanned childlessness, breastfeeding difficulties, and egg cryopreservation/donation.

A Department of Medicine Grand Rounds at the University of Pittsburgh was held to raise awareness of issues surrounding parenthood and to introduce the support network.**4** A best practice document was developed for support members, which included crisis and suicide network emergency contacts. There was also dissemination of the network both on physician and trainee listservs, as well as engagement of outside institutions to disseminate program implementation and solicit advice for future additions.

Breastfeeding/lactation support

Updated guidance by the American Academy of Pediatrics recommends breastfeeding for up to 2 years “as mutually desired by mother and child.”**5** Physicians and trainees who breastfeed can incur many challenges in achieving this recommended guidance. Prior to returning to work, one barrier includes low breastmilk supply.**6** This is an aspect of breastfeeding among physicians that is sparsely covered in studies amidst growing scientific evidence that focuses on benefits of breastmilk in both maternal and infant health. This can deeply impact physicians who may be well acquainted with the benefits of breastfeeding from the scientific literature, but data on low breastmilk supply is not adequately covered.

For cardiologists and trainees able and willing to breastfeed, additional barriers to recommended breastfeeding durations become apparent once returning to work. A prior survey by the American College of Cardiology noted that around 68% of cardiologists reported barriers to breastfeeding at work. Some of these barriers included trouble finding space to pump, time constraints for pumping, and trouble with low breastmilk supply.**6** The Mayo Clinic conducted a trainee-specific single center survey and found that half of trainees (including cardiology trainees) reported breastfeeding cessation prior to 6 months.**7** Several authors have undertaken approaches to address these barriers. At least one institution arranged for the location of lactation rooms, including portable/temporary units, close to procedural and operating room suites to accommodate physicians who have the greatest time constraints for pumping.

One academic medical center, the University of Pennsylvania, instituted a university-wide faculty lactation policy. This policy outlined a reduction in outpatient clinical effort equivalent to up to 30 minutes for every 4 clinical hours for up to 12 months after the birth of a child. It also mandated target relative value units to be prorated for leave as per allotted by the Family and Medical Leave Act. Further, it calls for equity on incentive opportunities otherwise available to faculty based on this prorated relative value units adjustment. Their strategic approach has been published for adaptation at other institutions.**8**

As noted, challenges around breastfeeding can impact trainees even more than practicing cardiologists. To help mitigate resource challenges, Vanderbilt University Medical Center obtained funding for at-work wearable breast pumps to be shared among physicians and physician trainees. In addition, a best practice document was created for resident trainees. This includes a stepwise approach to securing time for pumping during rotations. Support documents include letter templates to send for upcoming rotations to supervisors and established communication lines between the resident-parent and leadership advocates within medicine.

Focus areas for change

Improving insurance coverage for infertility treatment and cryopreservation

As noted, data suggest around 25% of birthing-capable physicians reported infertility diagnoses.**1** This exceeds the reported national 13% rate of infertility.**9** Investigations and treatment for infertility are often a time-consuming and expensive process. Physicians will often undergo numerous fertility specialist visits, lab work and imaging, followed by pharmacologic and invasive therapeutic interventions toward achieving a successful pregnancy. Prior surveys have noted costs from around $1,100 for fertility medications and exceeding $60,000 until pregnancy via in vitro fertilization was successfully achieved.**10**

These costs are typically unaffordable under trainee salaries and for young clinicians. A recent study collected information on insurance coverage for physicians among several top academic institutions throughout the country. They found many institutions do not provide enough coverage for even one cycle of in vitro fertilization, while many individuals require 3 or more cycles for successful egg retreival.**10** For those looking to preserve fertility via egg, embryo, or sperm cryopreservation, an even smaller percentage of academic medical institutions offered specific insurance coverage for cryopreservation.**10**

Rethinking bereavement leave

The United States is one of the few countries for which there are no policies to ensure paid parental leave. Time off for up to 12 weeks following the birth of a child, including adoption, or for the care of one's own medical condition is detailed under the Family and Medical Leave Act. However, there may be financial difficulties that result from this unpaid policy, which may compound if a trainee must extend their training time.

One solution may include expansion of these policies to include initiatives like flexible work hours. Bereavement policies exist among many training programs and hospital employers to offer time and support for physicians and their families following the loss of a partner or close family member. Pregnancy loss is not consistently included in these policies. While some physicians feel being at work with their colleagues may be helpful, they should be afforded flexibility and protected time if they prefer privacy. The current structure at most fellowships and health care institutions is such that you are either at work or not. This inflexibility can serve to create more stress for physicians who may only need short time periods off intermittently to attend therapy, support groups, or physician appointments. A progressive structure of paid time-off for bereavement in the setting of pregnancy loss should be offered by training programs and healthcare systems.

Directed counseling services

The emotional bereavement process following reproductive difficulties can be complex. As mentioned, the stigmatization of experiences including infertility and miscarriage can further complicate individual coping and support networks. Many hospitals and associated trainee programs have established confidential referral services. These include therapists and psychiatrists as well as peer-to-peer physician support.

Both trainee institutions and hospital systems should ensure their resources adequately cover support for these topics for both physicians and physician-trainees. Support resources and networks should be readily

accessible and available to their trainees. Trainees and practicing cardiologists should also be provided resources to help navigate the legal requirements of institutions and hospitals for pregnancy and parental leave, such as The Center for Work Life Law (www.worklifelaw.org).**2**

Conclusions

For cardiologists who choose to pursue parenthood, the road can be physically taxing, emotionally difficult, and financially burdensome. Cardiologists and cardiology-trainees must be provided with support, flexibility, and counseling resources to change a culture of silent coping with infertility, pregnancy, and postpartum complications toward a destigmatized, caring community at work. Those in leadership positions, specifically training program leadership, division leadership, and hospital administration, must create progressive parenthood policies and build robust support structures so that physicians and physician-trainees who encounter parenthood complications have the tools, financial/insurance coverage, and community network to overcome these hardships.