June Monthly News 2024

1. Uniform or Sex-Specific Cardiac Troponin Thresholds to Rule Out Myocardial Infarction at Presentation

BACKGROUND

Myocardial infarction can be ruled out in patients with a single cardiac troponin measurement. Whether use of a uniform rule-out threshold has resulted in sex differences in care remains unclear.

OBJECTIVES

The purpose of this study was to evaluate implementation of a uniform rule-out threshold in females and males with possible myocardial infarction, and to derive and validate sex-specific thresholds.

METHODS

The implementation of a uniform rule-out threshold (<5 ng/L) with a high-sensitivity cardiac troponin I assay was evaluated in consecutive patients presenting with possible myocardial infarction. The proportion of low-risk patients discharged from the emergency department and incidence of myocardial infarction or cardiac death at 30 days were determined. Sex-specific thresholds were derived and validated, and proportion of female and male patients were stratified as low-risk compared with uniform threshold.

RESULTS

In 16,792 patients (age 58 ± 17 years; 46% female) care was guided using a uniform threshold. This identified more female than male patients as low risk (73% vs 62%), but a similar proportion of low-risk patients were discharged from the emergency department (81% for both) with fewer than 5 (<0.1%) patients having a subsequent myocardial infarction or cardiac death at 30 days. Compared with a uniform threshold of <5 ng/L, use of sex-specific thresholds would increase the proportion of female (61.8% vs 65.9%) and reduce the proportion of male (54.8% vs 47.8%) patients identified as low risk.

CONCLUSIONS

Implementation of a uniform rule-out threshold for myocardial infarction was safe and effective in both sexes. Sex-specific rule-out thresholds should be considered, but their impact on effectiveness and safety may be limited.

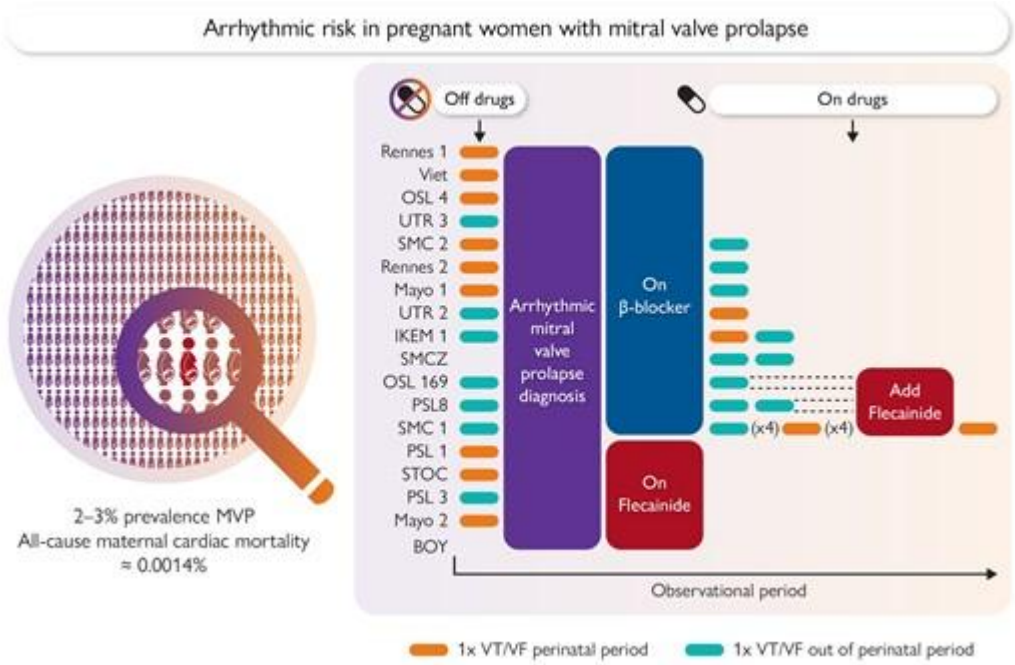
2. Differential sex-dependent role of lncRNAs in cardiomyopathy

Cardiovascular diseases are one of the most prevalent causes of mortality and morbidity worldwide. Structural diseases such as dilated and hypertrophic cardiomyopathy significantly contributed to it. In recent years, several studies have pinpointed the importance of non-coding genome in the pathogenesis of cardiomyopathy. We have previously reported the role of distinct lncRNAs in atrial fibrillation. We now explored the plausible role of these lncRNAs in cardiomyopathy by analyzing their expression in two different mouse mutant models of lamin (LMNA) - LMNAR249W and αMHCCreLMNAFF, a cardiac hypertrophic MyBPC3 mutant model as well as in experimental myocardial infarction mice. Importantly, both LMNA mutant models developed a dilated cardiomyopathy, a condition distinctly observed in males but not in females. Our data demonstrated that Walras, Gm26533, Wallrd, Walaa and Walrad are downregulated in females, but not males. Furthermore, differential deregulation is also observed in MyBPC3 mutant model but not in myocardial infarction. In vitro analyses demonstrated an estrogen-dependent regulation. In addition, expression analyses in distinct cardiovascular cell lines revealed enriched myocardial expression of Walras and Gm26533 while Wallrd and Walaa are preferentially expressed in endocardial cells. These data were further validated by in situ hybridization in embryonic cardiac tissues.

Walras overexpression resulted in enhanced expression of two key factors of UPR signaling pathway, i.e. Atf6 and Ire1, while Walras inhibition downregulated them. Upregulation of both UPR factors in Walrasgain-of-function assays is accompanied by increased cardiomyocyte apoptosis. In contrast, Walras inhibition resulted in increased Bcl2 expression and

therefore increased cell viability. Mechanistically, Walras directly interacts with calumenin protein, a known protective factor against UPR-associated apoptosis, as demonstrated by pulldown assays. In sum, we demonstrated sex-dependent regulation of distinct lncRNAs in different cardiomyopathic mouse models and at least one of them, i.e. Walras contributes to UPR-associated apoptosis regulation, providing a causative link to the development of distinct cardiomyopathies.

3. Arrhythmic risk in young women with mitral valve prolapse: keep your eyes open but don't jump at every shadow



Left panel: Mitral valve prolapse is frequent in the general population, but SCD as one cause of cardiac mortality related to MVP during the perinatal period is very rare. Right panel: Each of the 18 women included in the study is represented in one line. In the first column, an alphanumeric code indicates the institution which has included the patient. The majority of women presented with an out-of-hospital cardiac arrest while not taking anti-arrhythmic drugs, half of them during the perinatal period. Following the first episode, all were prescribed anti-arrhythmic drugs. Recurrences while on beta-blockers were very sporadic and mainly occurred outside the perinatal period. Of note, VT/VF recurrence occurred in only one of eight patients while on flecainide. Abbreviations: MVP, mitral valve prolapse; SCD,

sudden cardiac death; VT, ventricular tachycardia; VF, ventricular fibrillation

4. **Mitral valve prolapse: arrhythmic risk during pregnancy and postpartum**

Mitral valve prolapse (MVP) is the most common valvular abnormality with a prevalence of 2%–3% in the general population.1 Until recently, the prognosis of MVP patients was believed to be largely defined by the severity of mitral regurgitation and subsequent left ventricular dysfunction. Nevertheless, the association between MVP and sudden cardiac death was established decades ago,2,3 and recent studies have identified a specific subpopulation of MVP patients signified by a high risk of sudden cardiac death independent of mitral regurgitation severity and left ventricular function.4–6 This newly defined clinical syndrome is termed arrhythmic MVP (AMVP).7

In the original reports of AMVP, young women were over-represented, and the occurrence of malignant ventricular arrhythmia (VA) during child-bearing age poses challenges. Pregnant women with structural heart disease have an increased risk of VAs, particularly during the last trimester.8 Data regarding women presenting with AMVP and malignant VA during pregnancy or the postpartum period are scarce.8–10 However, one study showed an increased risk of cardiac arrest during pregnancy in patients with MVP compared to women without MVP.11 The incidence of malignant VA during a normal pregnancy in unselected patients is very low,12 but these events may have dire consequences to both mother and foetus.8,12,13

In this study, we aimed to assess if pregnancy and the postpartum period are associated with a higher risk of malignant VA. Therefore, we formed an international multi-centre cohort of high-risk AMVP patients who had experienced pregnancy to compare incidence of VA in perinatal vs. non-pregnant periods.

Methods

Study design and patient population

The data that support the findings of this study are available from the corresponding author upon reasonable request. This study was designed as a retrospective international multi-centre case series with data collected according to a standard case report form. A study protocol was designed by the lead investigators and approved by the ethics committees of the Sheba Medical Center and Oslo University Hospital. A list of potential collaborators in Europe, Asia, America, and Australia was created, and each centre was approached from August 2022 to April 2023, in a pre-designed way by email that included an abbreviated study protocol inquiring about potential cases of women over the age of 18 years diagnosed with AMVP who experienced pregnancy, study aims, and inclusion/exclusion criteria. Centres that expressed an interest in participating received the full set of the pre-approved documents including the study protocol and electronic case report forms for data collection.

In accordance with the European Heart Rhythm Association consensus document, AMVP was defined as presence of MVP, combined with frequent and/or complex VA in the absence of any other well-defined arrhythmic substrates.7 To be eligible for study inclusion, patients also needed to have one of the following: (i) documented ventricular fibrillation (VF), sustained ventricular tachycardia (VT), or appropriate shock from an implantable cardioverter defibrillator (ICD) during pregnancy or within 6 months after delivery or (ii) history of VF, sustained VT, or appropriate ICD shock and with follow-up data during pregnancy. Patients were not eligible for inclusion when other well-defined arrhythmic substrates or structural heart diseases were present. Pregnancy and postpartum period were defined as 9 months before and 6 months after delivery. The start of follow-up was defined as the date of AMVP diagnosis or the date of first malignant VA if the malignant VA occurred before the AMVP diagnosis.

De-identified individual patient data were collected from each participating centre using standardized forms. We collected data on the women's demographics, MVP diagnostic characteristics, pregnancy characteristics, Holter monitoring, electrocardiogram (ECG) QT interval measurements (mean, minimum, maximum, and corrected QT by Bazett's formula), malignant VA manifestations, and long-term outcomes. The study complied with the Declaration of Helsinki. We only included women who provided authorization for use of their data for research, and each centre was responsible for their patients' informed consent. Institutional review board approval was obtained at each participating institution.

Ventricular arrhythmia

Premature ventricular complex (PVC) burden was defined as % of PVC beats per 24 h assessed by Holter monitoring. T-wave inversion was defined as present if seen in ≥two adjacent ECG leads. Malignant VA was defined as either aborted cardiac arrest, VF, appropriate shock from an ICD, or sustained VT (>100 b.p.m. lasting >30 s). We defined non-sustained VT as ≥3 consecutive ventricular beats at a rate >100 b.p.m. lasting <30 s. Multifocal PVCs were defined as the presence of ≥3 different PVC morphologies on Holter monitoring.

Cardiac imaging

Mitral valve prolapse was diagnosed by echocardiographic or cardiac magnetic resonance imaging (CMR) before, during, or after pregnancy. Cardiac dimensions and functions were measured according to guidelines.14–16 We defined MVP as superior displacement ≥2 mm of any part of the mitral leaflet beyond the mitral annulus on echocardiography in the parasternal long-axis view.14 The mitral valve was defined as myxomatous if leaflet thickness was ≥5 mm. We defined mitral annular disjunction as ≥1 mm disjunction measured in end-systole from the left atrial wall–valve leaflet junction to the top of the left ventricular wall.17 Mitral regurgitation was evaluated by echocardiographic

examination at MVP diagnosis. Late gadolinium enhancement (LGE) by CMR was also documented when present.18

Statistical analysis

Continuous variables were presented as means with standard deviations or medians with interquartile ranges (IQRs) and categorical variables as absolute values with percentages. To explore whether the peripartum period was associated with increased incidence of malignant VA, we categorized each women's follow-up in two periods, a perinatal period (encompassing pregnancy and 6 months postpartum) and a non-pregnancy period, and summed the number of malignant VA events within each period. Due to the possibility of repeated events within one patient, we performed a univariate mixed-effects Poisson regression with random effect on individual level, accounting for time in each period. For ECG QT interval measurements, we used univariate mixed-effects linear regression with random effect on individual level (Stata/SE v16.1, StataCorp LLC, College Station, TX, USA). Due to the low number of patients, no statistical hypothesis testing was performed and no *P*-values were reported.

Results

Patient population

Out of the 27 centres approached for potentially eligible women, 12 centres had eligible women. We collected data on 26 women (range 1–5 per centre; *Figure 1*, Supplementary data online, *Table S1*). After detailed review, 8 women did not fulfil inclusion criteria and were excluded (all had only non-sustained VA). Thus, 18 eligible women [median age at AMVP diagnosis 24 (IQR 19–32) years] were included in this study, with median follow-up of 7.5 years (IQR 5.8–16.6) after AMVP diagnosis [*Table 1*; median 4.5 years (1.7–13.0) from AMVP diagnosis to first pregnancy and median 4.6 years (IQR 2.4–9.5) follow-up after first pregnancy]. Median age at first pregnancy after AMVP diagnosis was 29 years (IQR 27–34).

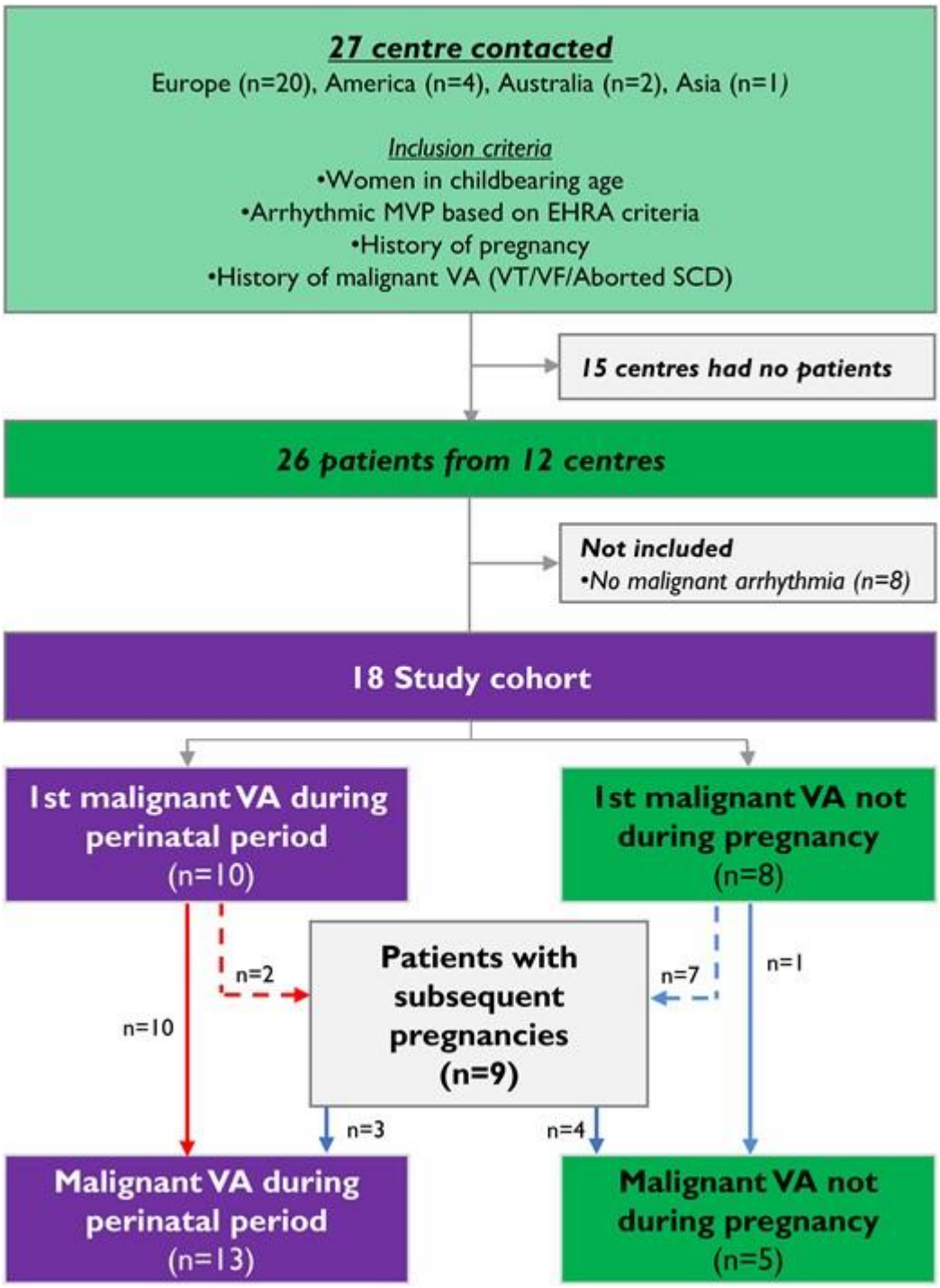


Figure 1

Study recruitment and inclusion chart. We contacted 27 centres from four different continents for possible collaboration on this case series, and we received 26 women with arrhythmic mitral valve prolapse from 12 centres. Eight women were not included due to not meeting predefined inclusion criteria. Thus, 18 women were included in this study

Table 1

Clinical characteristics of study participants

Characteristics	**Total (*n* = 18)**
Clinical characteristics	
Age at MVP diagnosis, years [IQR]	24 [19–32]
Number of pregnancies, *n* [IQR]	1.5 [1–2]
Pregnancy complicated by malignant VA, *n* (%)	13 (72)
Obstetrical complications, *n* (%)	3 (17)
Mode of delivery	
Vaginal delivery, *n* (%)	6 (55)
Caesarean section, *n* (%)	3 (27)
Othera, *n* (%)	2 (18)
T-wave inversions on ECG, *n* (%)	7 (41)
Aborted cardiac arrest, *n* (%)	15 (83)
Monomorphic VT, *n* (%)	5 (28)
Recurrent VT/VF, *n* (%)	10 (56)

Characteristics	**Total (*n* = 18)**
During pregnancy, *n* (%)	4 (22)
Cardiac symptoms	
Cardiac syncope, *n* (%)	7 (39)
Unexplained syncope, *n* (%)	2 (11)
Anti-arrhythmic drugs during pregnancy	12 (67)
Beta-blocker, *n* (%)	7 (39)
Flecainide, *n* (%)	1 (6)
Flecainide and beta-blocker, *n* (%)	3 (17)
Quinidine and beta-blocker, *n* (%)	1 (6)
Ablation for ventricular arrhythmia, *n* (%)	6 (33)
PVC-triggering VF ablation, *n* (%)	6 (100)
VT ablation, *n* (%)	2 (33)
Cardiac imaging	
MVP, *n* (%)	18 (100)
Barlow, *n* (%)	13 (76)

Characteristics	**Total (*n* = 18)**
Fibroelastic deficiency, *n* (%)	4 (24)
Inferolateral mitral annular disjunction (*n* = 13), *n* (%)	8 (62)
Left ventricular ejection fraction, %	57 ± 8
Mitral regurgitation	
No/trivial, *n* (%)	4 (22)
Mild, *n* (%)	6 (33)
Moderate, *n* (%)	7 (39)
Severe, *n* (%)	1 (6)
Late gadolinium enhancement (*n* = 10)	
No, *n* (%)	7 (70)
Left ventricular myocardium only, *n* (%)	2 (20)
Left ventricular papillary muscles only, *n* (%)	0 (0)
Both, *n* (%)	1 (10)
First reported Holter monitoring (*n* = 15)	

Characteristics	Total (*n* = 18)
Performed during pregnancy, *n* (%)	3 (20)
PVC burden, % per 24 h [IQR]	5.0 [0.5–9]
Multifocal PVCs, *n* (%)	10 (67)
PVC couplets, *n* (%)	13 (87)
Non-sustained VT, *n* (%)	10 (67)
Sustained VT, *n* (%)	0 (0)

MVP, mitral valve prolapse; MVA, malignant ventricular arrhythmia; PVC, premature ventricular complex; VT, ventricular tachycardia; VF, ventricular fibrillation.

One missed abortion and one terminated pregnancy.

All the women presented with aborted sudden cardiac death due to VF that required resuscitation and defibrillation. Most women had the myxomatous type of MVP, and moderate–severe mitral regurgitation was present in 8 patients (45%). T-wave inversions in the inferolateral leads were present in 7 women (41%). Data regarding mitral annular disjunction was only provided in 13 patients, of which 8 patients (62%) had inferolateral mitral annular disjunction. Cardiac magnetic resonance imaging was performed in 10 patients (56%), of which 1 was performed during pregnancy, 3 were performed in the postpartum period, and 6 were performed in the non-pregnancy period. Only 3 patients (30%) had LGE, of which 2 had left ventricular LGE only, while 1 had both left ventricular and papillary muscle LGE (*Table 1*).

Holter monitoring was reported in 15 women (83%), and the median PVC burden was 5.0% per 24 h (IQR 0.5–9.0); 10 women (67%) had multifocal PVCs and 10 (67%) had non-sustained VT. Premature ventricular complex–triggering VF ablation was performed in 6 women (33%), and 2 (11%) underwent simultaneous VT ablation.

Arrhythmic mitral valve prolapse diagnosis and malignant ventricular arrhythmias

There were 37 malignant VAs during the study period. In 6 (27%) women, the first malignant VA occurred before their first-ever pregnancy, 8 (36%) women had their first malignant VA during pregnancy or in the postpartum period, while 5 (28%) patients had malignant VA in non-pregnant periods only (*Figure 1*). Eighteen (49%) of the 37 malignant VAs occurred during the perinatal period in 13 (59%) women (*Figure 2*). The event rate was 0.15 events per patient-year in the non-pregnancy period and 0.59 per patient-year in the perinatal period. When subdividing the perinatal period, the event rate was 0.66 per patient-year during pregnancy and 0.48 per patient-year in the postpartum period.

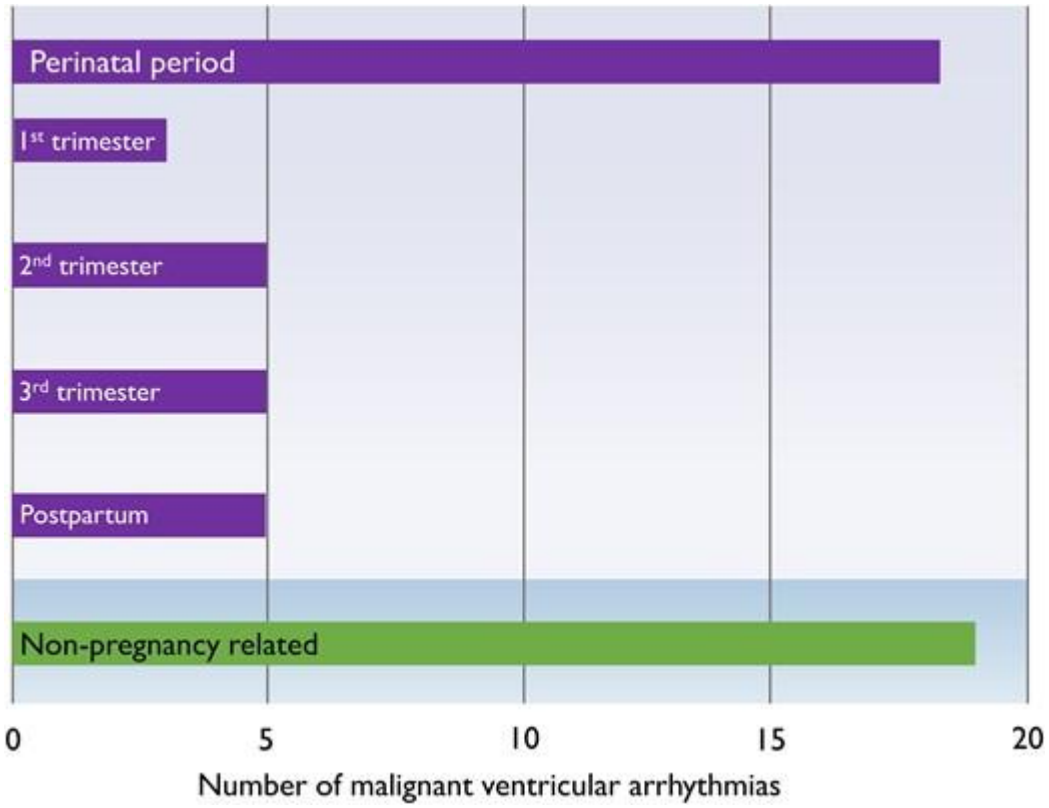


Figure 2

Distribution of 37 malignant ventricular arrhythmias during the perinatal and non-pregnancy periods. Thirty-seven malignant ventricular arrhythmias occurred in the 18 women in this study, of which 18 occurred in the perinatal period in 13 patients. The perinatal period had higher incidence rate of malignant ventricular arrhythmias

The perinatal period had an increased incidence rate of malignant VA compared to non-pregnancy periods in the same women [univariate incidence rate ratio (IRR) 2.66, 95% confidence interval (CI) 1.23–5.76]. However, upon examining the perinatal period through sub-analyses, we found that the postpartum period (IRR 2.54, 95% CI 0.93–6.94) and pregnancy (IRR 3.56, 95% CI 1.59–7.98) had both increased incidence rate of malignant VA with a numerically slightly higher risk during pregnancy. We found no difference in VA incidence between the different trimesters (*Figure 2*). Most malignant VAs were due to VF (n = 32, 87%), whereas only 5 (13%) events were sustained monomorphic VT, occurring in 5 unique women. None of the women died from the malignant VA.

Pregnancy characteristics

By definition, all included women experienced at least one pregnancy, and nine women experienced repeated pregnancies. Eight women (44%) were diagnosed with AMVP during the perinatal period due to malignant VA (*Figure 3*). One woman experienced a resuscitated cardiac arrest and miscarriage in gestational week 14, and another pregnancy was terminated at gestational week 8 due to multiple events of cardiac arrests requiring resuscitation. Despite malignant VA occurring during pregnancy, few obstetrical complications occurred, and the majority of deliveries were vaginal. Twelve (67%) women received prophylactic drug therapy during pregnancy, with beta-blockers most commonly used (*Table 1*). Only 9 of the 18 women had echocardiographic data during pregnancy. Of these, only 2 showed a change in mitral regurgitation severity and were both increased from mild to moderate. Only 1 woman had moderate–severe mitral regurgitation during pregnancy.

Individual level data on 18 women with arrhythmic mitral valve prolapse and pregnancy. A schematic overview of the 18 women included in this study (represented with one line) and the relationship between malignant ventricular arrhythmia (lightning symbol) occurring during pregnancy (orange bar), 6 months following delivery (black bar), or non-pregnant periods (light blue bar). Anti-arrhythmic therapies included beta-blockers (green bar), flecainide (red bar), and hydroxychloroquine (purple bar). The vertical line represents the time of arrhythmic mitral valve prolapse diagnosis. Malignant ventricular arrhythmia was reported 37 times, of which 13 women had malignant ventricular arrhythmia during the perinatal period

We collected 67 ECGs (42 during non-pregnancy and 25 during pregnancy) from our 18 women. The mean QTc during pregnancy was 425 ± 43 ms and during non-pregnancy 432 ± 24 ms. The QTc interval was slightly longer during pregnancy, but with wide CIs [6 ms (95% CI −15 to 28)]. QT

dispersion was numerically lower during pregnancy [−11 ms (95% CI −22 to 0)]. QTc was similar in women that experienced malignant VA during pregnancy compared to women that experienced malignant VA during non-pregnancy [0 ms (95% CI −35 to 36)]. QT dispersion was lower in women that experienced malignant VA during pregnancy [−23 ms (95% CI −45 to 0)].

Management strategies of malignant ventricular arrhythmias during pregnancy

An overview of the anti-arrhythmic therapies used can be found in *Figure 3* and Supplementary data online, *Figure S1*. Most patients continued the anti-arrhythmic medication used prior to pregnancy, and the dosage was not changed. Prior flecainide treatment was discontinued during pregnancy in three women, while three women continued prior use of flecainide during pregnancy with similar dosage. Prior beta-blocker use was continued during pregnancy in almost all women, except one that discontinued beta-blocker prior to pregnancy due to experiencing several miscarriages possibly related to beta-blocker use. Among the 10 women with a first malignant VA during the perinatal period, treatment of beta-blocker alone was started in 6, flecainide was started in 3 (of which 1 without beta-blocker), and 1 patient underwent VT and PVC ablation during pregnancy. Additionally, ICD implantation was performed in 9 women during the perinatal period, while implantation was postponed until after pregnancy in the woman undergoing ablation.

In patients with ICD who experienced ICD shock, no change in medication or dosage was performed.

Discussion

This is the first report evaluating the burden of VA events associated with the perinatal period in women with AMVP. In this multi-centre international case series of women with AMVP and a high-risk arrhythmic phenotype, we observed an increased incidence rate of malignant VAs during the perinatal

period as compared to non-pregnancy periods in the same women (*Structured Graphical Abstract*). This finding may be important in pre-conception counselling of women with AMVP, in decisions on anti-arrhythmic medication during pregnancy, and ultimately in decisions on primary prevention ICD implantations. Importantly, most pregnancies progressed to term with a low number of obstetrical complications.

By design, our cohort was very specific, focusing on young women of child-bearing age meeting the European Heart Rhythm Association criteria for AMVP.7 Our inclusion criteria yielded a high-risk group, where all patients had a history of malignant VA and even aborted sudden cardiac death. Risk factors in this cohort were similar to other high-risk AMVP groups,4,6 such as history of syncope, T-wave inversions, myxomatous MVP, and mitral annular disjunction. In contrast, our cohort had a surprisingly low proportion of women with LGE on CMR, though CMR was performed in only a subset of participants. Previous studies have reported LGE in 28%–36%19,20 with higher rates in patients with more severe mitral regurgitation.20 Our lower proportion of LGE may be explained by the young age of our participants, representing early stages of local remodelling, not yet progressing into replacement fibrosis. The fact that life-threatening arrhythmias occurred in several women without LGE is an important reminder that the absence of LGE is not necessarily a low-risk feature. Interestingly, five women in our study experienced monomorphic VT, where LGE is thought to represent the main substrate.

Pregnancy and the risk of arrhythmia

This study showed a seemingly increased incidence rate of malignant VA during the perinatal period compared to non-pregnancy in women with AMVP, with 2.5-fold higher incidence rate. This is in line with a prior observational study showing increased risk of maternal and foetal adverse outcomes during 23 000 pregnancies in women with MVP, with four-fold increased odds of cardiac arrest.11 Pregnancy, rather than the postpartum period, seemed to constitute the period of highest risk in our study. Whether

there is a true difference in risk between these periods remain to be explored in larger studies. However, even though the risk increases during pregnancy and the postpartum period, the absolute incidence rate of malignant VAs during the perinatal period in AMVP women remains low, as inferred by the very low number of cases found in 27 large medical centres.

The risk of malignant VA increases during the perinatal period in women with a variety of cardiac diseases, including structural heart disease and primary electrical disease.8,21 The mechanisms are multifactorial and include altered hormonal levels, haemodynamic changes, and an altered autonomic balance with predominantly sympathetic drive at rest.22 None of these alterations have been studied specifically in MVP, yet it may be reasonable to assume that some of these pathophysiological processes play a role in the AMVP population as well.

It has been postulated that mechanical traction and myocardial stretch caused by the prolapsing leaflet may be central to the arrhythmogenesis of MVP.23 Myocardial stretch may lead to a decrease in resting diastolic membrane potential, shortening of the action potential duration, and the development of stretch-induced early afterdepolarizations.24 These effects tend to be more pronounced in areas that are subjected to more traction,25 leading to action potential heterogeneities setting the stage for functional re-entry circuits. Pregnancy is associated with an increased effective circulating blood volume of up to 50%, possibly further accentuating these changes leading to a further increase in the risk of arrhythmia. Importantly, this mechanism may be independent of fibrotic substrates.26

Female sex hormones, especially oestrogen, affect cardiac repolarization causing QT prolongation, which is an expected observation in normal pregnancy.21,27,28 Interestingly, patients with AMVP tend to have longer QT than unselected patients with MVP,29 suggesting a similar vulnerability to the changes in the hormonal levels, possibly influencing the risk of VA.21

Pregnancy is also associated with altered pharmacokinetics of many medications30 in a progressive manner throughout pregnancy stages, which could explain the increased incidence of arrhythmic events seen in our study. Of interest, pregnancy is associated with increased activity of CYP2D6, which metabolizes many anti-arrhythmic drugs, including metoprolol, flecainide, and mexiletine. However, despite lower plasma concentrations of metoprolol during pregnancy, the chronotropic effect seems to be greater during pregnancy,31 suggesting altered sensitivity to metoprolol due to predominant sympathetic drive at rest during pregnancy.

Management implications

Thus far, guidance for the management of pregnant women with AMVP has been based on a limited number of case reports and expert opinions. Our findings have important implications that can inform the management of this complex clinical scenario and generate initial evidence to guide pre-conception counselling and arrhythmia surveillance during pregnancy. Women with AMVP who wish to become pregnant and their physicians should be aware of a potentially increased arrhythmic risk as observed in our study. In response, intensified arrhythmia surveillance approaches may be considered, aiming to capture precursors of malignant VAs such as high-risk PVCs and non-sustained VT. Finally, further studies should explore if a lower threshold for primary preventive ICD implantation should be considered in high-risk patients as part of pre-conception counselling. Furthermore, it is unknown whether surgical repair or replacement of severe mitral regurgitation decreases arrhythmic risk in AMVP patients. Whether prophylactic anti-arrhythmic drug therapy during pregnancy may be advisable in AMVP patients is yet to be explored. Both treating cardiologists and pregnant women may be reluctant towards anti-arrhythmic drugs due to possible risk to the foetus and mother. However, metoprolol, flecainide, and quinidine have long records of safety during pregnancy with minimal teratogenic effects and low foetal and maternal risk.32 These complex decisions are best made under the care of clinicians with expertise in AMVP in collaboration with maternal–foetal medicine in

tertiary care centres. While the retrospective case series nature of our report does not allow management recommendations, these data may provide general guidance for nuanced shared decision-making between patients and clinicians.

Study limitations

This is a retrospective observational study with inherent limitations with a low number of women affecting the robustness of the results. In order to avoid selection bias, we used a strict set of inclusion criteria resulting in a relatively homogenous high-risk cohort. We minimized differences in the intensity of medical care by beginning the follow-up at the time of AMVP diagnosis.

We included only women with AMVP patients that presented with malignant VA and were pregnant at least once. These narrow inclusion criteria reduce the applicability of these results to other AMVP populations. Similarly, our study design does not allow evaluation of the true attributable risk of the perinatal period. Furthermore, due to the retrospective nature, all women had to survive their index event to allow for diagnosis, extensive evaluation, and follow-up in order to be eligible for inclusion in this cohort. Nevertheless, our study design may be subject to recall bias, as healthcare providers may be more prone to remember pregnant patients with life-threatening events compared to non-pregnant patients. However, the design using each woman as her own control by comparing periods of pregnancy to non-pregnant periods may partly overcome this limitation.

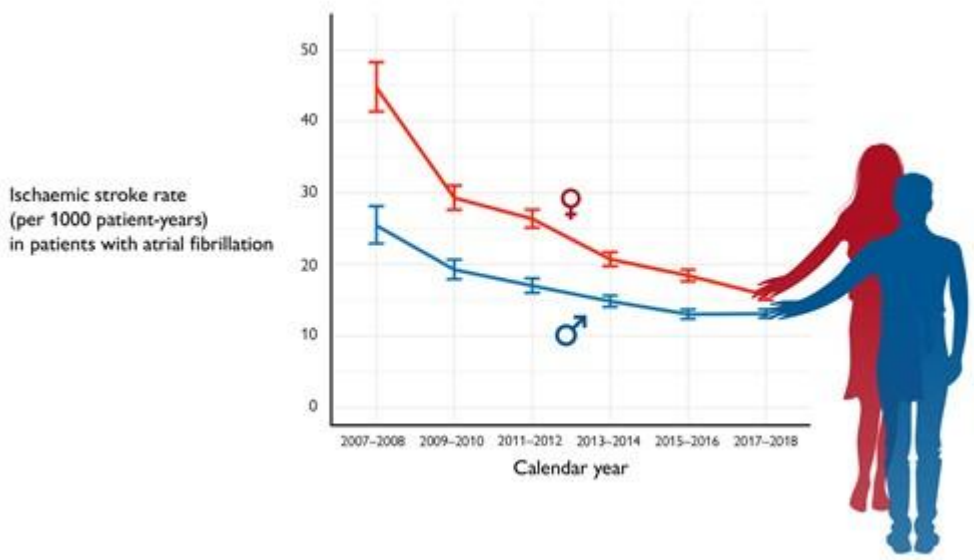
Some of the women in this study did not undergo CMR or Holter monitoring precluding any concrete conclusions regarding these aspects of the study. We were further limited in studying pregnancy related changes in function of the mitral apparatus and their association with arrhythmic risk, as repeat echocardiographic evaluation was available for only a few women in this study.

However, we believe that the design of our study using the women as their own controls limits the impact of recall bias and selection bias. Moreover, comparing events during pregnant and non-pregnant periods may partly overcome some of the inherent limitation. Finally, we do not have comparative echocardiographic, ECG, and Holter monitoring data during pregnancy and outside of pregnancy periods for the included patients.

Conclusions

The perinatal period could impose increased risk of malignant VAs in women with high-risk AMVP. Our data, although based on a small number of highly selected women that experience malignant VAs, may provide general guidance for pre-conception counselling and for nuanced shared decision-making between patients and clinicians. Further studies are needed to inform management of this population during pregnancy and in pre-conception counselling.

5.Taking the sex out of atrial fibrillation



6.Ischaemic stroke in women with atrial fibrillation: temporal trends and clinical implications

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting up to 5.2% of the adult population.1 It is a major cause of ischaemic stroke (IS), with the risk of stroke varying considerably among individuals based on their comorbidities and other characteristics.2,3 Accurate stratification of stroke risk and identification of individuals who would benefit from oral anticoagulant (OAC) therapy for stroke prevention is essential in managing patients with AF.

Women with AF are usually older and present with a higher burden of comorbidities than men, reflecting in higher IS rates in women.1,4,5 Additionally, female sex has been independently associated with risk of IS already in the early OAC trials and thereafter in observational studies.6,7 In 2010, the CHA_2DS_2-VASc stroke risk score, which included female sex as a factor, was proposed and subsequently adopted into international guidelines on AF management.2,8–10 However, the IS risk linked to female sex has an age dependency, and it is more a risk modifier in the presence of other IS risk factors.11–13 The connection between female sex and thromboembolic risk is believed to stem from a variety of factors related to both biologic sex and sociocultural gender, encompassing hormonal, structural, endocrine, lifestyle, and social components, but the precise pathophysiological mechanisms of this phenomenon have remained incompletely understood.14–16 Additionally, inequities in cardiovascular care have been shown to partly explain the higher stroke rates in women with AF.13

While the interplay between female sex and IS risk has been extensively studied, there is a paucity of information regarding the temporal trends in their association in patients with AF. Considering the intricate pathways underlying the elevated stroke risk in women, the advances in the optimal

management of other traditional stroke risk factors, and the historical trends in gender inequalities in both health and broader societal contexts, we hypothesized that the impact of female sex on the risk of IS in patients with AF has also changed over time. Thus, we conducted a nationwide cohort study covering all patients with incident AF in Finland between 2007 and 2018 to explore the temporal trends in IS risk associated with female sex.

Methods

The Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) study (ClinicalTrials Identifier: NCT04645537; ENCePP Identifier: EUPAS29845) is a nationwide retrospective cohort study that includes patients diagnosed with AF at all levels of care in Finland from 2004 to 2018.17 Patients were identified using all available national healthcare registers, including hospitalizations and outpatient specialist visits (HILMO), primary healthcare (AvoHILMO), and the National Reimbursement Register maintained by the Social Insurance Institute (KELA). The cohort inclusion criterion was an International Classification of Diseases, Tenth Revision (ICD-10), diagnosis code of I48, encompassing AF and atrial flutter, collectively referred to as AF, recorded between 2004 and 2018. Exclusion criteria were permanent emigration abroad before 31 December 2018 and age below 20 years at AF diagnosis. The present sub-study was conducted within a cohort of patients with incident AF from 2007 to 2018, established in previous studies of the FinACAF cohort.18–20 In this cohort, to include only patients with newly diagnosed AF, a washout period was applied by excluding those with a recorded AF diagnosis during 2004–06, because the medical history of <2 years was considered too short to exclude the presence of a prior AF diagnosis. Additionally, to ensure capturing the true initiation of OAC therapy and exclusion of patients with prior AF, those with a fulfilled OAC prescription during 2004–06 or within a year before the first AF diagnosis were excluded (see Supplementary data online, *Figure S1*).

The follow-up was primarily analysed with two separate approaches. In both methods, follow-up started from the initial AF diagnosis. In the first approach, we analysed the overall cohort with the entire follow-up continuing until the first observed IS event, death, or 31 December 2018, whichever came first. In this approach, analyses were adjusted for OAC use. Additionally, since it is the non-anticoagulated IS rate that drives the clinical decision-making of stroke prevention with OACs, in the second approach, we concentrated solely on the follow-up time without OAC therapy. In these analyses, follow-up continued only until the first OAC purchase, the first IS event, death, or 31 December 2018, whichever came first. The latter approach has been previously suggested for estimating event rates in untreated populations.21,22

Patients often develop new comorbidities after the initial diagnosis of AF, impacting the risk of IS and making their IS risk a dynamic process.23 To address potential bias associated with changing IS risk due to increasing age and incident comorbidities over a longer follow-up period, we also conducted analyses with a follow-up period restricted to a maximum of 1 year after the initial AF diagnosis, i.e. continuing until the occurrence of the first IS event, death, 31 December 2018, or a maximum of 1 year after AF diagnosis. Moreover, in these analyses of 1-year follow-up, we divided patients into categories based on their baseline stroke risk (low risk, CHA_2DS_2-VASc score 0 in men and 1 in women; moderate risk, CHA_2DS_2-VASc score 1 in men and 2 in women; high risk, CHA_2DS_2-VASc score > 1 in men and >2 in women; very high risk, CHA_2DS_2-VASc score > 2 in men and >3 in women). The analyses by risk category utilized the 1-year follow-up. Of note, the quality of the primary healthcare register (AvoHILMO) has been shown to be inferior to that of the well-validated hospital care register (HILMO), and patients with AF have been identified from reimbursement data increasingly after the introduction of direct OACs.24 To address potential selection bias arising from these factors, we conducted additional sensitivity analyses focusing exclusively on patients with AF identified from the hospital care register (HILMO), aligning with the approach commonly

employed in previous studies on IS rates in patients with AF.11,21,25 Data on baseline comorbidities were obtained from the aforementioned healthcare registers from all levels of care. The definitions of baseline comorbidities are presented in Supplementary data online, *Table S1*.

Outcomes

In patients without prior IS before or at the same date as the first AF diagnosis, IS event was considered to occur on the first date of a recorded I63 or I64 ICD-10 diagnosis code in the hospital care register after the cohort entry. In patients with prior IS before or at AF diagnosis, the event was considered to occur on the date of the first new hospitalization with I63 or I64 ICD-10 code as the main diagnosis with at least a 90-day gap from the prior event, which had occurred before AF diagnosis. Only IS diagnoses from the hospital register were included to ensure that the event of interest was truly major and clinically relevant.

Study ethics

The study protocol was approved by the Ethics Committee of the Medical Faculty of Helsinki University, Helsinki, Finland (nr. 15/2017), and received research permission from the Helsinki University Hospital (HUS/46/2018). Respective permissions were obtained from the Finnish register holders (KELA 138/522/2018, THL 2101/5.05.00/2018, Population Register Centre VRK/1291/2019-3, Statistics Finland TK-53-1713-18/u1281, and Tax Register VH/874/07.01.03/2019). Patients' personal identification numbers were pseudonymized, and the research group received individualized but unidentifiable data. Informed consent was waived due to the retrospective registry nature of the study. The study conforms to the Declaration of Helsinki as revised in 2013.

Statistical analyses

We estimated incidence rates and incidence rate ratios (IRRs) for IS using the Poisson regression model with a Lexis-type data structure based on

three time scales: follow-up time from AF diagnosis, calendar year in 2-year intervals, and age.26 This statistical method was chosen to compute IS rates for each calendar year interval and to account for patients' age increasing during the relatively long observation period between 2007 and 2018. With this method, patients' age at each point of follow-up was calculated. Subsequently, age was split into 5-year intervals and considered as a categorical variable in the analyses. Correspondingly, calendar years were divided into 2-year intervals. The adjusted analyses included the following variables: age, calendar year, heart failure, hypertension, diabetes, prior IS or transient ischaemic attack, vascular disease, dyslipidaemia, prior bleeding, alcohol use disorder, renal failure, liver cirrhosis or failure, cancer, dementia, psychiatric disorders, and income level (divided in tertiles). Additionally, in analyses, also including follow-up time with OAC use (i.e. the first approach described above covering the entire follow-up and the analyses on the 1-year follow-up after AF diagnosis), the adjusted analyses included also OAC use, with the follow-up time split according to OAC exposure. This exposure was considered to start from the first OAC purchase and continue until 120 days after the last drug purchase. The 120-day interval was chosen since in Finland it is possible to purchase drugs with reimbursement for a maximum of 90 days and an additional 30-day grace period was allowed to cover possible stockpiling and differences in warfarin dosing. Thereafter, we fitted the regression models with the interaction term between calendar year period and sex, to assess whether the association between sex and IS rate has changed over time. The x2 test, Student's *t*-test, and analysis of variance were used to compare baseline variables. Statistical analyses were performed with the IBM SPSS Statistics software version 28.0 (SPSS, Inc., Chicago, IL, USA) and R version 4.0.5 (R Core Team, Vienna, Austria; https://www.R-project.org).

Results

We identified 229 565 patients with new-onset AF (50.0% women; mean age 72.7 years; mean follow-up time 4.0 years; for comparison, the overall adult

population over 20 years of age in Finland in 2018 was 4.1 million). When compared with men, women were older and had higher burden of comorbidities and lower income, which were reflected also in their higher stroke risk scores (*Table 1*). The mean age at the time of AF diagnosis increased over time, particularly in men. Likewise, prevalence of comorbidities and the baseline stroke risk scores increased during the study period in both men and women, whereas the income disparities remained similar across the study period (see Supplementary data online, *Table S2*). Oral anticoagulant was initiated in 71.5% of women and 69.5% of men during follow-up. One-year mortality after the diagnosis of AF decreased continuously from 13.1% to 8.7% during the study period. The decrease was observed both in men and women, and mortality was constantly higher in women than in men (see Supplementary data online, *Table S3*).

Table 1

Characteristics of the study cohort

	Women	**Men**	***P*-value**
	***n* = 114 823**	***n* = 114 747**	
Mean age at baseline, years	76.6 (11.8)	68.9 (13.4)	<.001
Income tertiles			<.001
1st (lowest)	52 484 (46.0)	25 403 (22.1)	
2nd	38 162 (33.2)	38 162	

	Women	Men	*P*-value
	***n* = 114 823**	***n* = 114 747**	
		(31.8)	
3rd (highest)	23 813 (20.7)	52 858 (46.1)	
Highest education level			<.001
Primary school	67 816 (59.1)	52 561 (45.8)	
Upper secondary education	28 091 (24.5)	33 900 (29.5)	
Higher education	18 916 (16.5)	28 281 (24.6)	
Baseline comorbidities			
Any vascular disease	30 970 (27.0)	33 379 (29.1)	<.001
Diabetes	23 764	25	<.001

	Women	Men	*P*-value
	***n* = 114 823**	***n* = 114 747**	
	(20.7)	783 (22.5)	
Dyslipidaemia	56 321 (49.1)	53 331 (46.5)	<.001
Heart failure	22 199 (19.3)	17 718 (15.4)	<.001
Hypertension	92 288 (80.4)	77 966 (67.9)	<.001
Prior IS or TIA	19 267 (16.8)	16 108 (14.0)	<.001
Abnormal liver function	567 (0.4)	693 (0.6)	<.001
Abnormal renal function	4102 (3.6)	5028 (4.4)	<.001
Alcohol use disorder	1836 (1.6)	7226 (6.3)	<.001
Cancer	25 359	21	<.001

	Women	**Men**	***P*-value**
	***n* = 114 823**	***n* = 114 747**	
	(22.1)	893 (19.1)	
Dementia	7638 (6.7)	4140 (3.6)	<.001
Prior bleeding	10 442 (9.1)	14 097 (12.3)	<.001
Psychiatric disorder	15 342 (13.4)	15 656 (13.6)	.05
Risk scores			
Mean modified HAS-BLED score	2.6 (0.9)	2.4 (1.1)	<.001
Mean CHA_2DS_2-VASc score	4.2 (1.6)	2.6 (1.8)	<.001
Stroke risk categories			<.001
Low stroke risk	4926 (4.3)	14 205 (12.4)	
Moderate	12 277	20	

	Women	**Men**	***P*-value**
	***n* = 114 823**	***n* = 114 747**	
stroke risk	(10.7)	262 (17.7)	
High stroke risk	97 620 (85.0)	80 275 (70.0)	
OAC use during follow-up			
Any OAC	82 112 (71.5)	79 743 (69.5)	<.001
DOAC	25 414 (22.1)	26 743 (23.3)	<.001

The values represent counts (percentages) or means (standard deviations).

CHA_2DS_2-VASc score, congestive heart failure (1 point), hypertension (1 point), age ≥ 75 years (2 points), diabetes (1 point), history of stroke or TIA (2 points), vascular disease (1 point), age 65–74 years (1 point), and sex category (female) (1 point); DOAC, direct oral anticoagulant; IS, ischaemic stroke; modified HAS-BLED score, hypertension (1 point), abnormal renal or liver function (1 point each), prior stroke (1 point), bleeding history (1 point), age > 65 years (1 point), alcohol abuse (1 point), and concomitant antiplatelet/non-steroidal anti-inflammatory drugs (NSAIDs) (1 point) [no labile international normalized ratio (INR), max score 8]; TIA, transient ischaemic attack. Stroke risk categories based on CHA_2DS_2-VASc score: low,

0 in men and 1 in women; moderate, 1 in men and 2 in women; and high, >1 in men and >2 in women; OAC, oral anticoagulant.

Crude IS rates decreased considerably over the study period, particularly in women; however, the rates remained consistently higher in women (*Figure 1*). Female sex was associated with a higher IS rate in the unadjusted analyses, but not after adjusting for confounding factors. Similar associations emerged when considering the entire follow-up period, as well as when examining only periods without OAC use (*Table 2*). We observed an interaction between the calendar year period and sex (interaction term $P < .001$). There was a significant association between female sex and IS rate at the start of the study period. However, thereafter, an overall decreasing pattern in this association was observed, eventually becoming statistically non-significant by the end of the observation period. Notably, non-linear variability was observed in this decline. A similar attenuation of the stroke risk associated with female sex was observed in the analyses with and without OAC use (*Figure 2*). In the analysis focusing solely on a 12-month follow-up period following the diagnosis of AF, a comparable, yet more linear, decline in the association between female sex and the risk of IS was observed (*Figure 3*). In the sensitivity analyses covering only patients with AF diagnoses in the hospital setting, the findings were uniform to those of the analyses covering the overall cohort (see Supplementary data online, *Figure S3*).

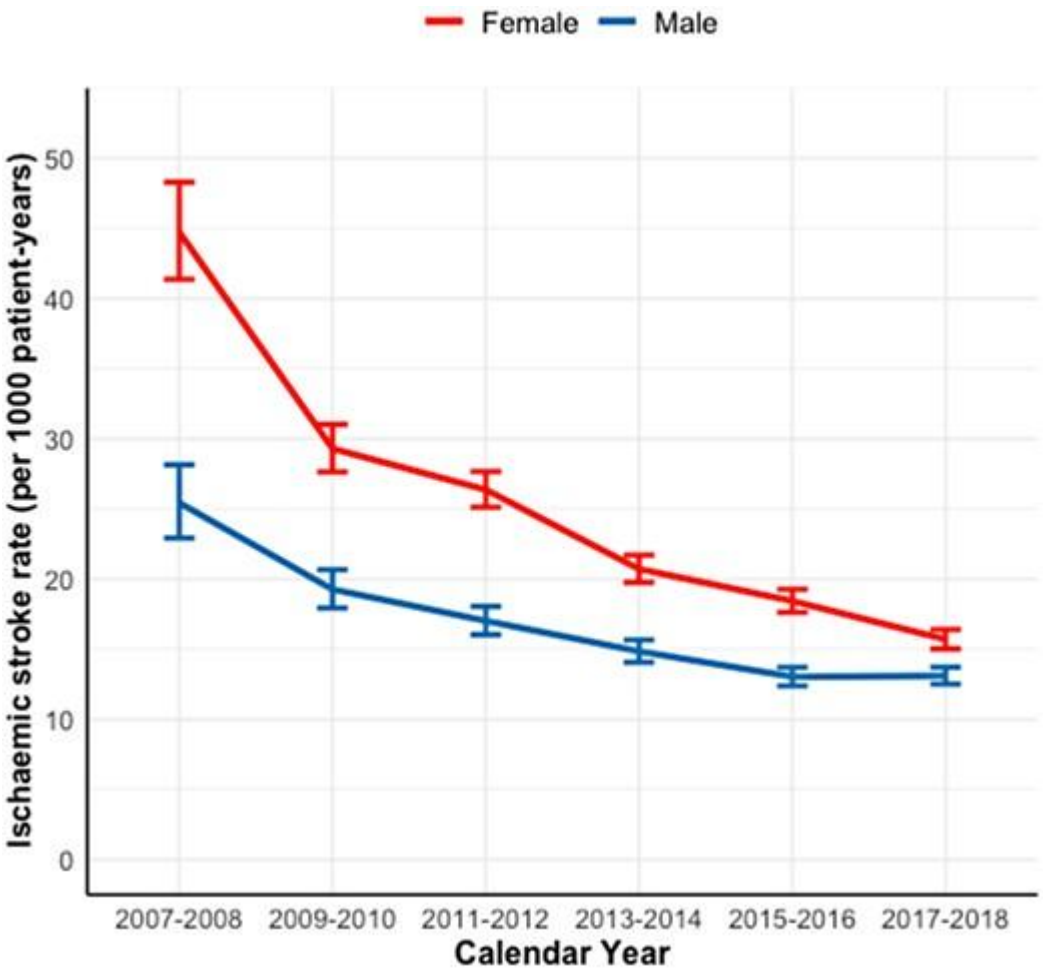


Figure 1

Trends in the crude ischaemic stroke rates with 95% confidence intervals in the entire follow-up

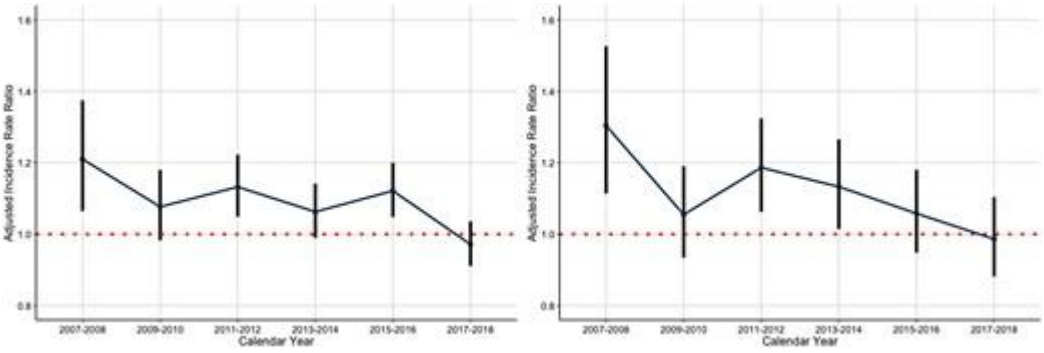


Figure 2

Adjusted incidence rate ratios of ischaemic stroke with 95% confidence intervals comparing women with men (red broken line) in the entire follow-up (left panel) and when considering only time without oral anticoagulant use (right panel)

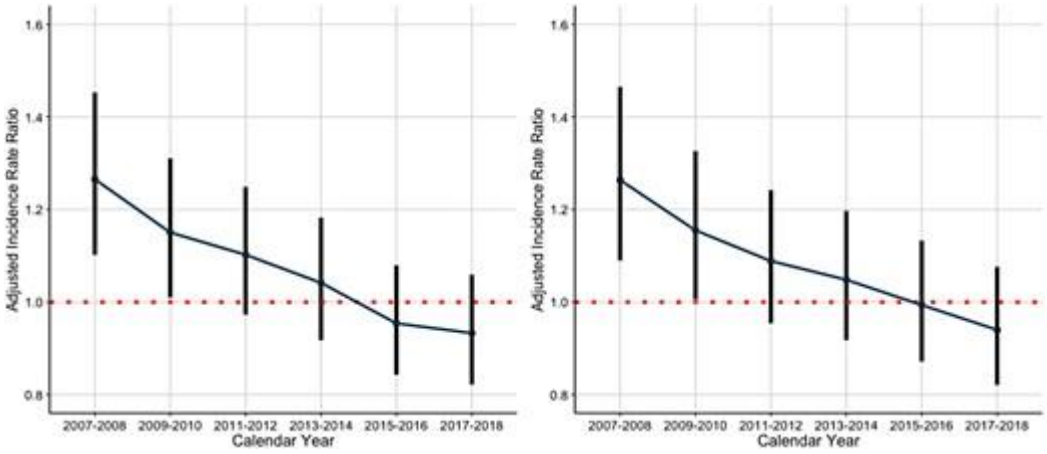


Figure 3

Adjusted incidence rate ratios of ischaemic stroke with 95% confidence intervals within a 1-year follow-up after atrial fibrillation diagnosis comparing women with men (red broken line) in the overall cohort (left panel) and in patients with high stroke risk (CHA_2DS_2-VASc score > 1 in men and >2 in women; right panel)

Table 2

Incidence of ischaemic stroke in men and women from 2007 to 2018

	Events	**Patient-years (1000 years)**	**Incidence (per 1000 patient-years)**	**Unadjusted IRR**	**Adjusted IRR**
Entire follow-up					
Men	6999	470	14.9 (14.5–15.2)	(Reference)	(Reference)
Women	9297	441	21.1 (20.7–21.5)	1.42 (1.37–1.46)	1.02 (0.99–1.06)
Follow-up without OAC use					

	Events	Patient-years (1000 years)	Incidence (per 1000 patient-years)	Unadjusted IRR	Adjusted IRR
Men	2986	174	17.2 (16.6–17.8)	(Reference)	(Reference)
Women	4136	141	29.4 (28.5–30.3)	1.71 (1.64–1.80)	1.05 (0.99–1.10)

95% confidence intervals in parenthesis. IRRs estimated by Poisson regression. Adjusted for calendar year period, age, hypertension, diabetes, heart failure, prior ischaemic stroke or transient ischaemic attack, vascular disease, prior bleeding, alcohol use disorder, renal failure, liver cirrhosis or failure, cancer, dementia, psychiatric disorders, and income level and OAC use.

IRR, incidence rate ratio; OAC, oral anticoagulant.

One-year outcomes by risk category

When analyses were stratified by stroke risk categories, female sex was associated with IS rate within the 1-year follow-up in the high-risk patient group (CHA_2DS_2-VASc score > 1 in men and >2 in women; Supplementary data online, *Table S4*). Similar to the analyses of the overall cohort, a significant interaction between the calendar year period and sex was observed in the high-risk group ($P < .001$), and the initially observed higher IS risk associated with female sex linearly decreased and became non-significant over the study period (*Figure 3*). These findings were reiterated also in patients classified as having a very high stroke risk (CHA_2DS_2-VASc score > 2 in men and >3 in women; Supplementary data online, *Figure S2*). In patients with low or moderate IS risk at baseline, no association between female sex and IS rate was observed (see Supplementary data online, *Table S4*). In these risk categories, the interaction terms between the calendar

year period and sex were non-significant (P = .84 for low risk and P = .87 for moderate risk), indicating the absence of significant temporal changes (see Supplementary data online, *Figures S4* and *S5*).

Discussion

This nationwide retrospective cohort study demonstrated that the IS risk independently associated with female sex in patients with AF has decreased over time during the study period from 2007 to 2018 (*Structured Graphical Abstract*). Initially, female sex was associated with a 20%–30% higher risk of IS in 2007–08, but by the end of the study period, this association became non-significant. When patients were stratified by stroke risk categories, a decline in IS risk associated with female sex was observed in more contemporary high-risk patients, becoming non-significant between females and males.

To the best of our knowledge, this is the first study to investigate temporal trends in the IS risk associated with female sex in patients with AF. Moreover, while the interplay between sex and IS risk has been extensively researched, the linkage of data from all national healthcare registries covering uniquely every level of care enables us to conduct substantially more robust and unbiased analyses than prior studies on this topic. Of note, the CHA_2DS_2-VASc score was originally generated from the Euro Heart Survey sample of only ~ 1000 patients with AF during 2003 and 2004 treated at hospital level.2 Likewise, subsequent larger observational studies exploring sex differences in stroke risk have relied on selected study samples from hospital-level data, predominantly from the early 2000s, and without accounting for possible confounding by socioeconomic factors.6,27 Thus, previous studies linking IS to female sex may have been susceptible to some selection, information, and confounding biases. Moreover, heterogeneity has been noted in the effect sizes among studies reporting the IS risks associated with female sex, reflecting differences in study designs and populations studied.6,27

We found that the crude IS rates decreased considerably during the study period, with a more pronounced decline observed among women. Although prior studies have not specifically addressed gender differences in IS trends among patients with AF, our findings are consistent with previous studies reporting improving prognosis of AF and decreasing overall stroke rates.28–31 Likewise, the magnitude of the observed decline in the overall IS rate is comparable with a Swedish study reporting a 42% decrease in IS rate from 2012 to 2018.30 In the beginning of the study period, female sex was associated with a 20%–30% higher IS rate, which corresponds with the effect sizes reported in previous meta-analyses.6,27 However, importantly, we observed that this association became non-significant with no difference between males and females in the more contemporary period, a finding previously unreported in any study.

Indeed, the association between female sex and IS rate exhibited an overall decreasing pattern in all of the adjusted analyses, although notably there was some variability in the analyses with longer follow-up times (*Figure 2*), as compared with the more linear trends observed in the analyses restricted to 1-year follow-up (*Figure 3*). The observed variability may thus stem from differences in follow-up duration, or represent natural fluctuations in IS incidence, or potentially be indicative of statistical fluctuation in the adjusted regressions. The attenuation in the association between female sex and IS was driven by the declining trends within the high stroke risk patient group, while in the low- and moderate-risk categories, female sex was not associated with a higher IS risk (see Supplementary data online, *Table S4*, *Figure 3*, and Supplementary data online, *Figures S3–S5*).

Taken together, the limited sex differences in IS amongst contemporary AF populations shown by the current FinACAF study cohort suggest that female sex could potentially be omitted as risk modifier when considering stroke risk stratification of patients with AF. Nevertheless, women tended to be under-treated with OACs in various observational studies and they sustain more severe IS events when they happen.32–35 Hence, consideration of female sex in stroke risk stratification might still draw

attention to the potentially increased AF-related stroke risks in women. However, we have previously reported a resolution of gender inequalities in OAC use over time, and correspondingly, sex-related disparities in OAC utilization have not been evident in more contemporary registries, as compared with older ones, such as the Euro Heart Survey.35–40

Analogous to the causes underlying the initial IS risk associated with female sex, the decline in this association is most likely related to several factors, many of which are not captured by the current data. The comprehensive nationwide data enable more thorough adjustments than most previous studies, but since the magnitude of the initial IS risk linked to female sex aligns with earlier findings, our results are unlikely to be attributable to differences in controlling for confounding factors compared with prior research. Thus, the trend of declining impact of female sex on stroke risk is most probably linked to other concomitant health trends, such as improvements in risk factor management and lifestyle-related factors. Indeed, there are reports suggesting diminishing gender inequalities in various aspects of health, although clear disparities still persist.41 Likewise, advances made in reducing gender inequalities in wider societal contexts, such as in socioeconomic conditions, may also contribute to the findings of this study.42 The use of OACs in patients with AF has increased substantially over the past decade.18,43 However, since we observed the decrease in the risk of IS associated with female sex also in the analyses that considered only the time when OACs were not used, this trend seems not to be exclusively linked to the improved utilization of OAC therapy. The prevalence of diagnosed comorbidities increased in both men and women during the study period, which may reflect increased screening for comorbidities and more holistic management of patients with AF, which has been associated with improved clinical outcomes, including a lowered risk of stroke.44,45 Moreover, previous studies have noted that part of the higher IS risk in women is linked to inequalities in cardiovascular care, and although the prevalence of comorbidities increased in both genders in our

study, decreasing inequalities in IS risk factor management may in part explain the findings of our study.13

Strengths and limitations

A particular strength of the current study is the nationwide coverage of patients diagnosed with AF from all levels of care, mitigating selection bias and therefore improving the generalizability of the results.17 Additionally, the hospital care register used to define the IS events is well-validated and has relatively high diagnostic accuracy, especially regarding cardiovascular diseases.46 Nevertheless, the limitations of our study need to be acknowledged, the most important of which are the challenges inherent in register-based retrospective cohort studies. Thus, information bias may be present in the used administrative data, potentially impacting the accuracy of recorded comorbidities and outcome events. We only considered IS events from the validated hospital care register to ensure the validity of the event, and although practically all patients with a suspected IS are examined in a hospital setting in Finland, some events may have been missed with this approach. Moreover, our results reflect associations and not necessarily causation between sex and IS. Our study comprehensively covers patients with AF in Finland, yet further research is needed to investigate whether similar trends have occurred in other countries. Except for diagnosed alcohol use disorders, the administrative data used lacked information about lifestyle-related factors. Additionally, we lacked data on the subtype of AF as well as data on adherence to OAC therapy. Moreover, we focused on event rates rather than risks since the current guidelines are mainly based on estimation of expected IS rates.10,47,48 Finally, although the linked registry data allowed us to adjust the regressions for a vast number of potentially influencing factors, the possibility of residual confounding by other unmeasured factors cannot be excluded, such as incident comorbidities and drug therapy changes.

Conclusion

In conclusion, the association between female sex and IS rate has decreased over time and become non-significant over the course of the study period from 2007 to 2018, suggesting that female sex could perhaps be omitted as a factor when estimating expected IS rates and the need for OAC therapy in patients with AF.

7. How Mediterranean Diets Might Cut Mortality in Women: New Insights

Women who adhere to the Mediterranean diet benefit from a survival advantage over time, partially driven by improvements in multiple cardiometabolic factors, according to new data from the Women's Health Study.

The findings add to prior evidence showing that the effects of a Mediterranean diet, which is heavy in unprocessed grains, fruits and vegetables, legumes, nuts, and olive oil and promotes seafood as the animal protein of choice, are just as strong in women as in men. But it also helps explain why.

"The current study is unique in being conducted prospectively over more than a quarter of a century and with very detailed evaluation of numerous risk factors and biomarker pathways," lead author Shafqat Ahmad, PhD (Brigham and Women's Hospital, Boston, MA), told TCTMD in an email. "Our study confirmed that the benefits on longevity extended long-term, and that modest changes in traditionally measured as well as novel risk factors accounted for part (but not most) of the benefit of the Mediterranean diet on all-cause risk and may have important downstream consequences for primary prevention."

Commenting on the study for TCTMD, Dariush Mozaffarian, MD, DrPH (Food is Medicine Institute at Tufts University, Boston, MA), said it confirms the real-world benefits of the Mediterranean diet that have been observed now in several randomized controlled trials.

“Importantly, the magnitude of the benefits is very similar to what was observed in the RCTs,” he said in an email. “Also importantly, the findings for the mediating biomarkers are entirely consistent with known physiologic benefits of the Med diet, strongly supporting causality of the findings.”

Because of this, Mozaffarian said, “it’s time to consider a Med Diet ‘standard of care’ for reducing cardiovascular and metabolic risk and apply it widely in clinical practice.”

Sarah Zaman, MBBS, PhD (The University of Sydney, Australia), who also commented on the study for TCTMD, agreed. While it wasn’t unexpected that the Mediterranean diet improved multiple cardiovascular risk factors, she said in an email, “what was surprising is that this effect did not seem to be mediated through the traditional major CVD modifiable risk factors of cholesterol (eg, LDL-C) or blood pressure.”

What is most important, Zaman added, is that the findings uncover more about the mechanisms behind this mortality benefit, as seen through lowering of small-molecule metabolites, inflammation, triglycerides, body mass index (BMI), and insulin resistance. “These all likely contribute to the known effect of a Med diet on lowering risk of CVD, death, and cancer and explain the mechanism of this effect,” she said, noting that it was “interesting” that the Mediterranean diet was not associated with substantial effects on traditional biomarkers like cholesterol or lipoprotein(a).

Mortality Benefits

For the study, published online last week in JAMA Network Open, Ahmad and colleagues included data from 25,315 participants in the Women’s Health Study (mean baseline age 54.6 years; 94.9% white) who were enrolled between 1993 and 1996 then followed for a mean of 24.7 years. The median Mediterranean diet adherence score—which ranges from zero to nine based on nine dietary components—was 4.0.

Overall, 3,879 participants died (24.1% due to CVD and 39.5% due to cancer) with mortality risk inversely associated with adherence to a Mediterranean diet. Specifically, compared with those with low adherence (score 0-3), those with middle (score 4-5) and high adherence (score 6-9) had lower adjusted risks of all-cause mortality (HR 0.84; 95% CI 0.78-0.90 and HR 0.77; 95% CI 0.70-0.84, respectively; P for trend < 0.001).

Reductions in cancer mortality were tied more closely to Mediterranean diet adherence than were drops in CVD mortality, with the highest scores (≥ 6) associated with a 17% reduced risk of CVD mortality (HR 0.83; 95% CI 0.69-0.99; P for trend = 0.03) and a 20% reduced risk of cancer mortality (HR 0.80; 95% CI 0.69-0.92; P for trend = 0.002).

These risk reductions remained significant when the models were further adjusted for lifestyle factors like smoking, physical activity, alcohol intake, and menopause status for both the middle (HR 0.92; 95% CI 0.85-0.99) and upper adherence groups (HR 0.89; 95% CI; 0.82-0.98; P for trend = 0.001).

Of the 33 biomarkers the researchers examined, small molecule metabolites and inflammatory biomarkers contributed most to the lower mortality risk, explaining 14.8% and 13.0% of the total risk, respectively. Triglyceride-rich lipoproteins (10.2%), BMI (10.2%), and insulin resistance (7.4%) also contributed substantially. But biomarkers like branched-chain amino acids, high-density lipoproteins, low-density lipoproteins, glycemic measures, and hypertension each contributed to less than 3% of the total risk.

“We were not expecting such a long-term consistent benefit that was over a quarter of a century based on what women reported eating so many years before,” Ahmad said. “It was interesting also that the biomarkers related to small metabolites, inflammatory markers, triglyceride-rich measures, insulin resistance, and adiposity were potentially explaining some of the benefit.”

But since the biomarkers they looked at could not explain the totality of the survival advantage associated with the Mediterranean diet, Ahmad said it’s

likely that additional factors “are also involved in benefit, such as the gut microbiome, neurohormonal regulation, and/or other pathways.”

Other Mechanisms?

Zaman was pleased with the results but predicted they won’t change clinical practice, as the Mediterranean diet “is already the most recommended diet in guidelines and clinical cardiology.”

Still, this study “paves the way for future research into understanding the mechanisms for dietary intake on cardiovascular disease risk,” she said. “It also is exciting in that it suggests that diet could be individualized in the future. For example, a Mediterranean diet clearly has major effects on inflammation and, in individuals where this is the main driver for CVD, it could have huge benefits. However, in individuals where the main driver for CVD is elevated LDL cholesterol, then perhaps a different dietary pattern would have a larger impact.”

Future work into the additional unknown mechanisms at play are also warranted, according to Zaman. “As is evident from other work, residual CVD risk exists, and future work needs to identify new risk factors and biomarkers for CVD,” she said, adding that dietary studies in more diverse groups of participants are also needed.

Ahmad said he would specifically like to see more studies explore “vascular endothelium markers, arterial stiffness and vulnerability, gut microbiome, [and] neurohormonal regulation.” Also, he said, “it will be important to see how changes in the diet relate to benefit.”

8. Overweight in Teens, Young Adults Tied to Cerebrovascular Disease in Women

Non-traditional cardiovascular risk factors may have an important impact on adverse pregnancy outcomes. In identifying rheumatoid arthritis (RA) as an independent risk factor for maternal cardiovascular complications, Zahid et al. highlight the importance of gaining additional insight into the

impact of non-traditional cardiovascular risk factors on pregnancy outcomes. Being overweight in adolescence or early adulthood is associated with an increased risk for cerebrovascular disease among women, according to a study published online June 6 in Stroke.

Ursula Mikkola, from the University of Oulu in Finland, and colleagues conducted a prospective cohort study to examine the effect of body mass index (BMI) and its changes in adolescence and young adulthood (ages 14 and 31 years) on early-onset cerebrovascular disease through age 54 years in a study including 10,491 people.

During follow-up, 452 individuals (4.7 percent) experienced cerebrovascular disease. The researchers found that compared with normal weight, the risk for ischemic cerebrovascular disease was increased at ages 14 and 31 years for women with overweight (hazard ratios [95 percent confidence intervals], 2.49 [1.44 to 4.31] and 2.13 [1.14 to 3.97], respectively) and obesity (hazard ratios [95 percent confidence intervals], 1.87 [0.76 to 4.58] and 2.67 [1.26 to 5.65], respectively). The results were independent of BMI at earlier or later time points. Men did not have similar associations. Women and men with obesity had an increased risk for hemorrhagic cerebrovascular disease at age 31 years (hazard ratios [95 percent confidence intervals], 3.49 [1.13 to 10.7] and 5.75 [1.43 to 23.1], respectively). At age 14 years, the risk for any cerebrovascular disease related to overweight was 2.09 times higher among girls than boys. At age 31 years, the risk for ischemic cerebrovascular disease related to obesity was 6.96 times higher among women than men.

"The association between childhood overweight and adult cerebrovascular disease is independent of overweight or obesity in adulthood, highlighting the importance for children to achieve and maintain healthy weights," the authors write.

9.Heavy Cannabis Use Linked to CVD Mortality in Women

Heavy cannabis use is associated with a significantly increased risk for cardiovascular disease (CVD) mortality among women, according to a study published online June 6 in JAMA Network Open.

Alexandre Vallée, M.D., Ph.D., from Foch Hospital in Suresnes, France, examined sex-stratified associations of cumulative lifetime cannabis use with all-cause, CVD, and cancer mortality using data from volunteers in the U.K. Biobank population. Data were included for 121,895 participants.

During a median follow-up of 11.80 years, Vallée identified 2,375 total deaths, including 1,411 and 440 deaths from CVD and cancer, respectively. After full adjustment, in men, the hazard ratios (95 percent confidence intervals) were 1.28 (0.90 to 1.81), 0.98 (0.43 to 2.25), and 1.09 (0.71 to 1.67) for all-cause mortality, CVD mortality, and cancer mortality, respectively, for heavy cannabis users versus nonusers. In women, the corresponding hazard ratios (95 percent confidence intervals) after full adjustment were 1.49 (0.92 to 2.40), 2.67 (1.19 to 4.32), and 1.61 (0.91 to 2.83) among heavy cannabis users versus nonusers. Heavy cannabis use was associated with a significantly increased risk for all-cause mortality, CVD mortality, and cancer mortality in female current tobacco users and with CVD mortality among female never tobacco users, after full adjustment. Heavy cannabis use was associated with a significantly increased risk for cancer mortality in male current tobacco users.

10.Exploring Sex Differences in LBBAP vs. BIVP For CRT

Similar clinical outcomes were observed among men and women undergoing left bundle branch area pacing (LBBAP) for CRT, and men undergoing LBBAP had a lower risk of heart failure (HF)-related hospitalizations and all-cause mortality when compared to men undergoing biventricular pacing (BIVP), according to a study presented at Heart Rhythm 2024 and simultaneously published in JACC: Clinical Electrophysiology.

Usha B. Tedrow, MD, MSc, et al., set out to explore sex differences in response to LBBAP vs. BIVP for CRT, including a total of 539 patients (69.7% men, 30.3% women) with left ventricular ejection fraction (LVEF) ≤35% and LBBB or an LVEF ≤40% with an expected right ventricular pacing exceeding 40% undergoing initial CRT with LBBAP or BIVP. The composite primary outcome was HF-related hospitalization and all-cause mortality.

Results showed no significant difference in the primary outcome when comparing men vs. women undergoing CRT with LBBAP (p=0.46). Among the BIVP group, the primary outcome was more frequent in men than women (p=0.03).

The primary outcome occurred 29.9% in men undergoing LBBAP and jumped up to 46.5% of men undergoing BIVP (p=0.004), while the difference noted among women (24.14% for LBBAP and 36.2% for BIVP) was not statistically significant (p=0.23).

The authors also looked at all procedure-related complications, finding no significant differences by sex. The most common complications among the LBBAP group were lead dislodgement (7.1%) with 3.5% requiring reintervention, and device-related infections (2.7%). In the BIVP group, most common complications included lead dislodgement (4.8%), with all of them requiring reintervention, and phrenic nerve stimulation (4.2%).

“Despite being underrepresented in trials, female sex is recognized as a predictor of success in HF patients eligible for CRT using BIVP…” write the authors. “Our results showed that men undergoing LBBAP as the initial CRT strategy had a similar clinical outcome in comparison to women in the LBBAP and BIVP groups (p=0.46), overcoming the previously recognized sex differential response to BIVP.”

11.Little Progress in Women Authorship in Four Major CV Journals Over Past Decade

Study authors **Ridhima Goel, MD**, **Roxana Mehran, MD, FACC**, et al., for the Women as One Scientific Expert Panel, analyzed 19,503 papers published from Jan. 1, 2010, to Dec. 31, 2019, by four cardiovascular journals: JACC, European Heart Journal, JAMA Cardiology (only included since its first issue in 2016) and Nature Reviews Cardiology. Researchers assessed gender identity manually through online searches. Any papers containing authors whose gender identity could not be confirmed were excluded from the final analysis.

Results showed that of the 111,562 total authors for the 18,535 papers in the final analysis, only 20.6% were women – and nearly half of the papers (47.7%) did not list any women as authors. Conversely, only 6.2% of papers listed no men as authors.

Over the study period, there was little significant change in the proportion of papers with at least one woman as an author, except for an increase in review papers (49.3% to 61.2%) while there was a decrease for woman authorship of "other" or miscellaneous papers (59.8% to 6.6%).

Editorials represented the category for which there was the lowest proportion of women as authors – they accounted for only 14.8% of all editorial authors, and only 23.3% of editorial articles featured a woman author. Research papers had the highest proportion of women authors at 21.8%. Guidelines had the highest proportion of work – 84.7% of all guidelines had at least one woman as an author.

Women accounted for 18.8% of first authors and 11.9% of last authors on papers with at least two authors. The proportion of women as middle authors was highest in papers with women as first and last authors (37.8%) and lowest in papers with men as first and last authors (19.8%).

Looking at the progress by geography, of the 62 countries surveyed, women were <1% of the first authors in 45 countries and <1% of last authors in 34 countries. More women as first authors were affiliated with institutions in the U.S. (34.6%) and the UK (25.2%), and more women were last authors who were affiliated with institutions in the U.S. and the Netherlands (6.5%).

Given that publication productivity is an important metric for promotions in cardiology, gender inequalities in publications not only affect the individual career trajectories of women but also have broader implications for the field's diversity and inclusivity, note the authors. "A call to action is needed to promote women in cardiology and provide them with equitable opportunities," they write.

Proactive measures are needed such as ACC's internal medicine cardiology programs including one targeted to women, along with continuing the work of ACC's Women in Cardiology Member Section, the Diversity and Inclusion Committee and the annual Women in Cardiology Leadership Workshop, along with programs through Women as One and others.

In an accompanying editorial comment, **Mary Norine Walsh, MD, MACC**, and **JoAnn Lindenfeld, MD, FACC**, call the study an insight into the "MANuscript," twin to the more familiar concept of the "manel"– an all-male conference panel. "Although the organizers of many cardiovascular conferences have gone to great lengths to ensure the absence of manels," Walsh and Lindenfeld write, "very few cardiovascular journals have made efforts to ensure diversity in the author block."

Among their recommendations to address this issue is calling for the medical publishing industry to institute blinded peer review, increase diversity on journal editorial boards, stress diverse authorship in editorial policies, extend invitations for reviews and editorials to a more diverse group of experts, and track their progress by a more frequent review of metrics.

12. Geographic Mapping of Gender Disparities in Authorship of Cardiovascular Literature

Background

Women in cardiology experience considerable gender disparities in publications, which hinders their career advancements to higher faculty and senior leadership positions. However, the extent of these disparities across different types of cardiovascular literature is not well understood.

Objectives

We investigated gender differences in authorship across various cardiovascular publications over a decade and examined geographic variations in the representation of women authors.

Methods

All papers published from January 1, 2010, to December 31, 2019, in 4 major cardiovascular journals (*Journal of the American College of Cardiology*, *European Heart Journal*, *Journal of the American Medical Association Cardiology*, and *Nature Reviews Cardiology*) were reviewed.

Results

Of the 18,535 papers with 111,562 authors, 20.6% of the authors were women, and 47.7% of the papers had no women authors. Over 10 years, the proportion of women authors remained low (20.7% in 2010 to 21.4% in 2019), with the lowest proportion in editorial papers (14.8%) and the highest in research papers (21.8%). More women as first (34.6%) and last (47.6%) authors were affiliated with institutions in the United States compared with other countries. The proportion of women middle-order authors was higher on papers with women as first authors (29.4% vs 20.5%) or last authors (30.6% vs 21.3%), compared with papers with men as first or last authors, respectively.

Conclusions

Over the past decade, the proportion of women authors across all article types in major cardiovascular journals remained low. A call to action is needed to promote women in cardiology and provide them with equitable opportunities.

12.Addressing the Global Burden of Cardiovascular Disease in Women: JACC State-of-the-Art Review

Cardiovascular diseases (CVDs) are responsible for approximately 35% of all deaths in women. In 2019, the global age-standardized CVD prevalence and mortality of women were 6,403 per 100,000 and 204 per 100,000, respectively. Although the age- and population-adjusted prevalence has decreased globally, opposite trends are evident in regions of socioeconomic deprivation**.** Cardiovascular health and outcomes are influenced by regional socioeconomic, environmental, and community factors, in addition to health care system and individual factors. Cardiovascular care in women is commonly plagued by delayed diagnoses, undertreatment, and knowledge gaps, particularly in women-specific or women-predominant conditions. In this paper, we describe the global epidemiology of CVD and highlight multilevel determinants of cardiometabolic health. We review knowledge and health care gaps that serve as barriers to improving CVD outcomes in women. Finally, we present national, community, health care system, and research strategies to comprehensively address cardiometabolic risk and improve outcomes in women.

Highlights

- CVD is the leading cause of death in women worldwide.
- Regional variation in CVD burden reflects socioeconomic determinants.
- A multilevel approach is required to improve cardiometabolic health and

CVD outcomes in women on a global scale.

13.The Oxygen Cascade According to HFpEF Likelihood: A Focus on Sex Differences

Introduction

Reducing the burden of heart failure with preserved ejection fraction (HFpEF) poses a major health care challenge. The majority of patients affected by HFpEF are women.**1** Diagnosing HFpEF is complex, often arising from unexplained dyspnea requiring a complex series of evaluations to determine its underlying cause.**2-4** Despite improvements in diagnostic algorithms, many patients with exertional breathlessness remain uncategorized, especially in female cohorts.**2-4** By the time HFpEF is diagnosed, women experience lower exercise tolerance (peak oxygen uptake [VO2]) than men, greater limitation of daily activities, and increased rates of frailty, leading to reduced quality of life.**5-7** Sex-specific differences in pathophysiology (eg, increased sensitivity to afterload) and response to therapies highlight the need to understand sex disparities, which have been underappreciated due to the underrepresentation of women in key trials.**8-10** Prior studies indicate that women with HFpEF have smaller ventricles, exaggerated increases in mean pulmonary artery pressures/cardiac output (mPAPs/CO), higher left ventricular (LV) afterload, and decreased peak exercise stroke volume (SV), CO, and skeletal muscle oxygen extraction.**8**,**9**,**11** However, the use of invasive hemodynamics measures limited these studies to small, selected cohorts, leaving uncertainty regarding sex disparities in larger, more diverse patient populations with symptoms suggestive of HFpEF. Moreover, similar sex-related differences in peak VO2, cardiac structure, and cardiac function are also seen in healthy individuals,**1** making it unclear whether sex differences in exercise intolerance in individuals with or at risk for HFpEF reflect female physiology or sex-related differences in pathophysiology. Consequently, the mechanisms underpinning women's lower exercise tolerance across the

continuum from unexplained dyspnea to HFpEF remain unclear.**1** To address this gap, our study aimed to comprehensively and noninvasively investigate sex differences in peak VO2 and its Fick principle-derived determinants in patients with unexplained dyspnea according to differing HFpEF probabilities. We hypothesized that regardless of their diagnostic HFpEF scores, women would have reduced peak VO2 due to impairments at multiple steps along the O2 cascade, including decreased O2 delivery and extraction.**12**

Methods

Study design

This was a secondary analysis of an ongoing patient cohort study designed to investigate the clinical and physiological characteristics of patients referred to a multidisciplinary dyspnea clinic. The detailed study design and methodology, and primary outcomes discussing the utility of this clinic for evaluation of HFpEF and unexplained dyspnea have been published previously.**13**,**14** The study obtained approval from the local ethics committee (JESSA ethische toetsingcommissie, 2022/014).

Study sample

We analyzed consecutive patients referred to a dedicated dyspnea clinic (Jessa Ziekenhuis, Hasselt, Belgium) between January 2016 and December 2022 who presented with exertional dyspnea or fatigue (**Supplemental Figure 1**). Patients with a LV ejection fraction <50% or HFpEF mimickers (pericardial disease, congenital heart disease, high-output heart failure, and infiltrative, restrictive, or hypertrophic cardiomyopathy) were excluded.**4**,**14** Additionally, patients with more than mild established pulmonary disease or significant valve lesions (including any mitral stenosis, more than mild primary mitral regurgitation, more than mild aortic regurgitation, more than moderate aortic stenosis and severe tricuspid and functional mitral regurgitation) were excluded.

Dyspnea clinic protocol

The dyspnea clinic utilized a standardized work-up as previously described, including clinical evaluation and chart review, laboratory testing, spirometry test, transthoracic echocardiography, 12-lead electrocardiogram at rest, and cardiopulmonary exercise test combined with exercise echocardiography (CPET*echo*).**14** The spirometry yielded the forced expiratory volume per second (FEV1) over forced vital capacity. Maximal voluntary ventilation was calculated as the FEV1 multiplied by 40. Breathing reserve was calculated by measuring the ratio of peak ventilation to estimated maximal voluntary ventilation. Iron deficiency was defined as ferritin <100 µg/L and transferrin saturation <20% with ferritin 100 to 300 µg/L.

Cardiopulmonary exercise test with exercise echocardiography

All patients underwent a maximal, symptom-limited, semi-supine bicycle test with simultaneous continuous respiratory gas analysis and echocardiography (ie, CPET*echo*) using a ramp protocol (5-20 W/min) designed for the patient to achieve an exercise duration of 8 to 10 min.**14-17** The protocol was personalized to the patient's age, weight, and functional class by dividing the maximal load during a previous upright exercise test by 10 (rounded down). Breath-by-breath VO2, carbon dioxide production, tidal volume, and respiratory rate were continuously recorded. Patients were monitored with a 12-lead electrocardiogram, pulse oximetry for peripheral capillary O2 saturation, and cuff blood pressure throughout exercise and recovery. Echocardiographic views and Doppler samples were obtained at rest, intermediate and peak exercise, as previously described.**18** Briefly, the load was kept constant when passing the first ventilatory threshold but always with a heart rate <100 beats/min until the intermediate exercise set of echocardiographic measures were obtained (for 2-3 minutes). Then, the ramp protocol was continued until exhaustion. Shortly before reaching peak exercise (onset of severe symptoms, aiming for a respiratory exchange ratio >1.10), the load was kept constant (for a shorter time; 0-1 minutes) for the second time to obtain the peak exercise

data set. The mPAP/CO slope was calculated as previously described and validated by invasive exercise hemodynamics.**18**

HFA-PEFF and H2FPEF scores to determine HFpEF likelihood

A positive HFpEF score was defined as a total HFA-PEFF score ≥5 or a H2FPEF ≥6. A positive diastolic stress test added 3 or 2 points to the total HFA-PEFF score, whether or not the tricuspid regurgitation velocity during exercise was >3.4 m/s. Agitated colloid (1-3 mL) was routinely injected intravenously, as described previously, to improve feasibility and accuracy of the tricuspid regurgitant velocity measurement (**Supplemental Figure 2**).**18**

Fick principle determinants of peak VO2

The Fick components comprised CO and arteriovenous O2 extraction (a-vO2diff). SV was estimated by the time velocity integral of the flow at the left ventricular outflow tract multiplied by the surface area or 0.785 × aortic annulus diameter.**2** CO was calculated as: SV × heart rate. Oxygen delivery was calculated as: CO × arterial O2 content (CaO2) (calculated as hemoglobin × arterial O2 saturation × 1.34). Peak a-vO2diff was determined as peak exercise VO2 divided by CO. Arteriovenous O2 extraction values are reported unadjusted and adjusted for hemoglobin concentration, while muscle O2 diffusive conductance (DmO2) was estimated noninvasively as previously described and illustrated in **Figure 1**.**19-21** In brief, mixed venous O2 content was calculated as CaO2–a-vO2diff. Estimated DmO2 was then calculated as peak VO2–venous O2 content. Resting arterial elastance was calculated as 0.9 × systolic blood pressure x SV, while LV stiffness was calculated as: E/e′ ÷ LVEDV (LV end-diastolic volume).**22**

Noninvasive Wagner Diagram

The interplay between O2 delivery (dotted line) and O2 diffusion (solid lines) in females and males with unexplained dyspnea. Fick Principle and law of diffusion determinants of peak VO2 for males vs females (Peak VO2: 20.8 in

males vs 16.3 mL/kg/min in females; 32% lower in females) are represented by a modified the Wagner diagram. The average non-invasive estimation of CvO2 on the x-axis was 15% higher in females (6.0 vs 5.2 mL/dL), while O2 delivery (peak CaO2 x peak CO) corrected for body weight was 10% lower in females (23.9 vs 26.5 mL/kg/min). The Fick's diffusion law slope (estimated muscle diffusive oxygen conductance, DmO2 = VO2 ÷ CvO2) line is 32% lower in females. Estimated DmO2 reflected O2 diffusion and utilization more accurately than CvO2 or a-vO2Diff since DmO2 corrects for the shorter capillary transit time associated with the higher cardiac output in males. Arrow A shows the hypothetical effect of increasing female O2 delivery to the male level with a constant O2 diffusion (DmO2 slope). CvO2 would increase (and avO2Diff decrease) because of a shorter capillary transit time, and VO2 would increase marginally. Only a combined optimization of O2 delivery and DmO2 (arrow A + B) up to the level of males would allow females to reach equivalent male values for peak VO2. CvO2 = peak mixed venous O2 content (CaVO2 - a-vO2Diff); CaO2 =peak arterial O2 content (hemoglobin × 1.34 × peak SpO2); a-vO2Diff = peak arterio-venous difference in O2 content (peak VO2 ÷ peak cardiac output); DmO2 = estimated O2 diffusion from capillary to mitochondria (VO2 ÷ CvO2); O2 delivery = cardiac output x SpO2 × hemoglobin × 1.34.

Statistical analysis

Females and males were compared in the: 1) total cohort; and 2) according to HFpEF likelihood (positive or negative HFpEF score). Continuous variables were expressed as the mean ± SD for normally distributed data or median (IQR) for non-normally distributed data. Categorical data were expressed as numbers and percentages and compared with the Pearson chi-square test or Fisher's exact test when appropriate. Continuous variables in 2 groups were compared with the Student's *t*-test or Mann-Whitney *U* test, while ANOVA with post hoc testing (Tukey test) was used for more than 2 groups (males vs females across HFpEF likelihood groups). Mean differences were reported with 95% confidence intervals. Univariable and multivariable linear regression was employed to identify the association between age, sex

and Fick determinants (hemoglobin, peak exercise SV, heart rate, arterial O2 saturation, and a-vO2diff) with cycling power-to-weight ratio (as an alternative to peak VO2, as a-vO2diff values are directly calculated from peak VO2 and therefore violate the assumption of independence) and peak VO2. Multicollinearity was tested with the variance inflation factor. Statistical significance was defined as at a 2-tailed probability level of <0.05. All statistics were performed using Jamovi (version 2.3).

Results

Cohort characteristics

The final cohort included 1,963 patients with unexplained dyspnea (mean age: 64 ± 15 years; n = 951, 49% women; mean BMI: 27 ± 5 kg/m2, 22% obese) (**Tables 1** and **2**). Average peak VO2 was 18.6 ± 8.6 mL/kg/min (77% ± 23% predicted), hemoglobin of 13.8 ± 1.5 g/dL, and a median N-terminal prohormone B-type natriuretic peptide of 130 (52-300) ng/L. Mean FEV1 over forced vital capacity was 0.80 ± 0.13, and their FEV1 was 83% ± 22% of the predicted. FEV1 was similar between sexes (P = 0.13), but women had a higher ratio of forced FEV1/forced vital capacity (Tiffenau index, P < 0.001) and were less likely to be active or former smokers than men (P = 0.003 for both). Both the median (IQR) HFA-PEFF score (including the points attributed by exercise echocardiography) and H2FPEF score were 2 (1-4). HFpEF was likely in 29% of patients (n = 555) based on a positive HFA-PEFF or H2FPEF score, with a significantly higher proportion of females (34%, n = 321) compared to males (24%, n = 234) from the total cohort classified with a positive HFpEF score (P = 0.001). The use of negative inotropic drugs was comparable in males and females.

Table 1Total Unexplained Dyspnea Group: Sex Differences in Demographics	**N**	**Total (N = 1,936, 100%)**	**Females (n = 951, 49%)**	**Males (n = 985, 51%)**	**Mean Difference (95% CI)**	***P* Value**
Age, y	1,936	64 ± 15	65 ± 14	63 ± 15	2 (1-3)	0.003
Height, cm	1,936	170 ± 10	163 ± 7	175 ± 8	−13 (−12 to −14)	<0.001
Weight, kg	1,936	77 ± 15	71 ± 14	83 ± 14	−12 (−13 to −11)	<0.001
Body surface area, m2	1,936	1.9 ± 0.2	1.8 ± 0.2	2.0 ± 0.2	−0.2 (−0.2 to −0.3)	<0.001
Body mass index, kg/m	1,936	27 ± 5	27 ± 5	27 ± 4	-	0.731
Obesity (BMI >30 kg/m)	1,936	430 (22)	240 (25)	190 (19)	–	0.002
Atrial fibrillation	1,936	329 (17)	146 (15)	178 (18)	–	0.109
Diabetes mellitus	1,932	247 (13)	109 (11)	138 (14)	–	0.093
Hypertension	1,936	856 (44)	428 (45)	428 (43)	–	0.491
Negative chronotropic drug	1,652	444 (47)	403 (48)	374 (46)	–	0.370
Respiratory characteristics						
Smoking active	676	65 (10)	30 (8)	35 (13)	–	0.003
Smoking	676	135	69 (17)	66	–	0.003

Table 1Total Unexplained Dyspnea Group: Sex Differences in Demographics	**N**	**Total (N = 1,936, 100%)**	**Females (n = 951, 49%)**	**Males (n = 985, 51%)**	**Mean Difference (95% CI)**	***P* Value**
former		(20)		(24)		
FEV1/FVC	1,782	0.80 ± 0.13	0.82 ± 12	0.78 ± 14	0.04 (0.02-0.05)	<0.001
FEV1, %	1,787	83 ± 22	84 ± 21	82 ± 22	2 (4-0)	0.129
HFpEF scores						
H2FPEF score	1,936	2 (1-4)	3 (1-4)	2 (1-4)	–	0.075
Logistic H2FPEF score	1,936	42 (24-70)	44 (26-74)	39 (22-67)	–	0.001
HFA-PEFF score	1,936	2 (1-4)	2 (1-5)	2 (1-4)	–	<0.001
Positive HFpEF scorea	1,936	555 (29)	321 (34)	234 (24)	–	0.001
Positive HFA-PEFF score	1,936	468 (24)	278 (29)	190 (19)	–	<0.001
Positive H2FPEF score	1,936	219 (11)	120 (13)	99 (10)	–	0.07
Laboratory results						
NT-proBNP, ng/L	1,118	130 (52-300)	150 (68-310)	100 (50-258)		<0.001
eGFR CKD-EPI, mL/min/1.73	1,517	78 ± 23	76 ± 22	80 ± 23	−4 (−2 to −6)	<0.001

Table 1Total Unexplained Dyspnea Group: Sex Differences in Demographics	N	Total (N = 1,936, 100%)	Females (n = 951, 49%)	Males (n = 985, 51%)	Mean Difference (95% CI)	*P* Value
m2						
HBA1c, %	1,034	5.8 ± 0.7	5.7 ± 0.7	5.8 ± 0.8	−0.1 (0 to −0.2)	0.035

Values are mean ± SD, n (%), or median (IQR).

P values for post hoc group comparison female vs male.

BMI = body mass index; FEV1 = forced expiratory volume in 1 second; FEV1/FVC = forced expiratory volume in 1 second/forced vital capacity; GFR = estimated glomerular filtration rate calculated according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula; H2FPEF = (Heavy; Hypertensive; atrial Fibrillation; Pulmonary hypertension; Elder; Filling pressure) score; HbA1c = glycated hemoglobin; HFA-PEHFA-PEFF = Heart Failure Association Pretest probability Echocardiography, Functional testing, Final diagnosis; NT-proBNP = N-terminal prohormone B-type natriuretic peptide.

a A positive HFpEF score was defined as a total HFA-PEFF score ≥5 or a H2FPEF ≥6. A negative HFpEF score was defined as a total HFA-PEFF score <5 or a H2FPEF <6.

Table 2Total Unexplained Dyspnea Group: Sex Differences in Rest and Peak Exercise Values	N	Total (N = 1,936, 100%)	Females (n = 951, 49%)	Males (n = 985, 51%)	Mean Difference (95% CI)	*P* Value
Exercise capacity						
Respiratory exchange ratio (RER)	1,807	1.11 ± 0.11	1.10 ± 0.11	1.11 ±	−0.02 (−0.01 to	<0.001

Table 2Total Unexplained Dyspnea Group: Sex Differences in Rest and Peak Exercise Values	**N**	**Total (N = 1,936, 100%)**	**Females (n = 951, 49%)**	**Males (n = 985, 51%)**	**Mean Difference (95% CI)**	***P* Value**
				0.11	−0.03)	
Load/weight, W/kg	1,869	1.4 ± 0.8	1.2 ± 0.7	1.6 ± 0.9	−0.4 (−0.3 to −0.5)	<0.001
Peak VO2, mL/kg/min	1,837	18.6 ± 8.6	16.3 ± 7.1	20.8 ± 9.3	−4.4 (−3.7 to −5.1)	<0.001
Peak VO2 (Wasserman), % pred	1,837	72 ± 23	75 ± 22	71 ± 23	+4 (2-6)	<0.001
Peak VO2 peak (Gläser), % pred	1,829	77 ± 23	77 ± 23	77 ± 23	-	0.70
Cardiac morphology						
LA volume index, mL/m2	1,739	25 ± 11	25 ± 12	24 ± 11	+1 (2-0)	0.20
End-systolic LA/LV volume, %	1,421	149 ± 100	178 ± 104	131 ± 93	+37 (−27 to 47)	<0.001
LV end-diastolic volume index rest, mL/m	1,478	51 ± 16	46 ± 13	55 ± 16	−9 (−8 to −10)	<0.001
LV mass index, g/m2	1,728	83 ± 26	78 ± 31	90 ± 37	−12 (−9 to −14)	<0.001
Relative wall thickness	1,739	0.43 (0.37-0.51)	0.43 (0.36-0.51)	0.43 (0.38-0.51)		0.07
Diastolic LV internal diameter, mm	1,743	45 ± 7	43 ± 6	47 ± 7	−4 (−3 to −4)	<0.001

Table 2Total Unexplained Dyspnea Group: Sex Differences in Rest and Peak Exercise Values	**N**	**Total (N = 1,936, 100%)**	**Females (n = 951, 49%)**	**Males (n = 985, 51%)**	**Mean Difference (95% CI)**	***P* Value**
RV end-diastolic area, cm2	1,504	18 ± 5	16 ± 5	20 ± 5	−4 (−4 to −5)	<0.001
Rest and exercise cardiac function						
LA booster function by LACI (mL/s/m/cm)	1,128	3.4 (2.2-5.1)	3.5 (2.3-5.3)	3.2 (2.2-5.0)		0.08
MAPSE rest, mm	797	10 ± 3	9 ± 3	10 ± 3	−1 (−1 to −2)	<0.001
MAPSE peak, mm	780	13 ± 3	12 ± 3	14 ± 3	−2 (−2 to −3)	<0.001
Arterial elastance rest (Ea), mm Hg/mL	1,845	2.0 ± 0.5	2.1 ± 0.6	1.8 ± 0.5	0.2 (0.2-0.3)	<0.001
E/e’ rest	1,912	11 ± 5	12 ± 5	10 ± 4	+2 (1-2)	<0.001
E/e’ intermediate exercise	1,902	11 ± 5	12 ± 5	11 ± 4	+1. (1-2)	<0.001
LV stiffness (E/e’/LVEDV), mL−1	1,864	0.13 ± 0.08	0.16 ± 0.09	0.10 ± 0.06	+0.06 (0.05-0.07)	<0.001
mPAP/CO slope, mm Hg/L/min	1,936	3.0 ± 2.0	3.2 ± 2.1	2.8 ± 1.7	+0.5 (0.3-0.7)	<0.001
exTRV, m/s	1,934	3.4 ± 0.4	3.4 ± 0.3	3.4 ± 0.4	−0 (0 to −0.1)	0.003
RVFAC, %	1,002	48 ± 50 ± 11		47 ±	3 (2-4)	<0.001

Table 2Total Unexplained Dyspnea Group: Sex Differences in Rest and Peak Exercise Values	**N**	**Total (N = 1,936, 100%)**	**Females (n = 951, 49%)**	**Males (n = 985, 51%)**	**Mean Difference (95% CI)**	***P* Value**
		11		11		
TAPSE, mm	973	17.0 ± 5.5	16.8 ± 5.4	17.9 ± 5.2	−1.1 (−1.8 to 0.5)	<0.001
TAPSE/sPAP, mm/mm Hg	973	0.83 ± 0.68	0.82 ± 0.63	0.92 ± 0.82	−0.10 (−0.20 to −0.01)	0.024
RVESPAR, mm Hg/cm2	1,004	2.9 ± 1.4	3.3 ± 1.5	2.4 ± 1.1	0.9 (0.8-1.1)	<0.001
LV end-diastolic volume index peak, mL/m2	1,846	51 ± 15	46 ± 13	56 ± 16	−9 (−8 to −11)	<0.001
LV ejection fraction rest, %2	1,883	62 ± 8	63 ± 8	62 ± 8	+1 (1-2)	<0.001
LV ejection fraction peak, %	1,423	69 ± 10	69 ± 10	68 ± 10	+1 (2 to −0)	0.20
Stroke volume index rest, mL/m2	1,935	37 ± 9	37 ± 9	38 ± 10	−1 (0 to −2)	0.10
Stroke volume index peak, mL/m2	1,936	45 ± 10	44 ± 9	47 ± 11	−3 (−2 to −4)	<0.001
Stroke volume peak, mL	1,936	86 ± 21	78 ± 17	93 ± 21	−15 (−14 to −17)	<0.001
Heart rate peak, beats/min	1,936	127 ± 25	126 ± 25	127 ± 23	−1 (2 to −3)	0.518
Heart rate reserve, %	1,936	65 ± 24	65 ± 25	66 ± 23	-	0.50
Cardiac output	1,936	10.9	±9.8	±11.8	−2.0 (−1.7	<0.001

Table 2Total Unexplained Dyspnea Group: Sex Differences in Rest and Peak Exercise Values	**N**	**Total (N = 1,936, 100%)**	**Females (n = 951, 49%)**	**Males (n = 985, 51%)**	**Mean Difference (95% CI)**	***P* Value**
peak, L/min		3.4	2.9	± 3.6	to −2.3)	
Oxygen delivery, L/min	1,495	1.9 ± 0.7	1.7 ± 0.6	2.2 ± 0.8	−0.5 (−0.4 to −0.6)	<0.001
Cardiac index peak, L/min/m2	1,827	5.8 ± 1.8	5.6 ± 1.7	5.9 ± 1.9	−0.4 (−0.2 to −0.5)	<0.001
Noncardiac factors						
a-vO2Diff, mL/dL	1,822	12.9 ± 3.8	11.5 ± 3.0	14.3 ± 4.0	−2.9 (−2.5 to −3.2)	<0.001
a-vO2Diff/Hb	1,542	0.93 ± 0.27	0.87 ± 0.23	1.01 ± 0.28	−0.14 (−0.11 to −0.17)	<0.001
Cardiac output/VO2 slope	1,835	5.6 ± 2.1	6.1 ± 2.2	5.2 ± 2.0	+0.9 (0.8 to 1.1)	<0.001
Mixed venous saturation, %	1,484	27 ± 20	32 ± 17	22 ± 20	+11 (9-13)	<0.001
Hemoglobin, g/dL	1,574	13.8 ± 1.5	13.2 ± 1.2	14.4 ± 1.6	−1.2 (−1.0 to −1.3)	<0.001
Transferrin saturation, %	1,201	27 ± 12	26 ± 12	29 ± 13	−4 (−3 to −5)	<0.001
Iron deficiency	1,219	541 (44)	349 (55)	192 (33)		<0.001
Ve/MVV	1,793	0.60	0.60 ± 0.18	0.60 ± 0.20	-	0.30
SpO2	1,777	98 (96-	98 (96-99)	97 (96-	+0 (0-1)	0.001

Table 2Total Unexplained Dyspnea Group: Sex Differences in Rest and Peak Exercise Values	N	Total (N = 1,936, 100%)	Females (n = 951, 49%)	Males (n = 985, 51%)	Mean Difference (95% CI)	*P* Value
		99)		98)		

Values are mean ± SD, median (IQR), or n (%).

Sex differences in peak VO2 and its determinants in the total cohort presenting with unexplained dyspnea

Women with unexplained dyspnea had a lower peak VO2 and cycling power-to-weight ratio than men with unexplained dyspnea (16.3 ± 7.1 mL/kg/min vs 20.8 ± 9.3 mL/kg/min; 1.2 ± 0.7 W/kg vs 1.6 ± 0.9 W/kg, $P < 0.001$ for both) (**Central Illustration**, **Tables 1** and **2**, **Supplemental Figure 3**). The lower peak VO2 was associated with reduced O2 delivery (1.7 ± 0.6 L/min vs 2.2 ± 0.8 L/min, $P < 0.001$) and a-vO2diff (11.5 ± 3.0 mL/dL vs 14.3 ± 4.0 mL/dL, $P < 0.001$). Regarding O2 delivery, women had lower hemoglobin (13.2 ± 1.2 g/dL vs 14.4 ± 1.6 g/dL, $P < 0.001$) and peak exercise CO (9.8 ± 2.9 L/min vs 11.8 ± 3.6 L/min, $P < 0.001$). Furthermore, their lower peak exercise CO was due to a smaller SV (78 ± 17 mL/beat vs 93 ± 21 mL/beat, $P < 0.001$) as peak heart rate was similar between groups (126 ± 25 beats/min vs 127 ± 23 beats/min, $P = 0.52$). Women had a smaller peak SV even when indexed for body size (44 ± 9 mL/m2 vs 47 ± 11 mL/m2, $P < 0.001$). Finally, in addition to a lower hemoglobin concentration, the reduced a-vO2diff in women in the total cohort was mediated by a lower DmO2 (**Figure 1**). Results were similar when excluding patients in atrial fibrillation at the time of testing (n = 56; 3% of the total cohort), as well as those with a history of atrial fibrillation (n = 315, 16% of the total cohort).

Sex Differences Across the Oxygen Cascade in Patients With Unexplained Dyspnea: Negative vs Positive HFpEF Scores

HFpEF = heart failure with preserved ejection fraction.

Sex differences in individuals with a positive HFpEF score

Similar sex differences were observed in patients with both low and high HFpEF scores as in the total cohort (**Central Illustration**, **Figure 2**, **Table 3**). In 28% of the total cohort (n = 555), HFpEF was considered likely, with a higher proportion (58%) with a positive HFpEF score being women. Patients with a positive HFpEF score (H2FPEF score ≥6 or HFA-PEFF score ≥5 points) had lower peak VO2 and its determining Fick principle components than those with a negative HFpEF score (**Figure 2**). Compared to men with a positive HFpEF score, women with a positive HFpEF score had lower peak exercise a-vO2diff, CO, SV, and hemoglobin. Peak heart rate and O2 saturation showed no significant differences. Like in the total cohort, women with a positive HFpEF score had worse exercise tolerance (peak VO2 13.1 ± 4.1 mL/kg/min vs 15.9 ± 5.5 mL/kg/min, $P < 0.001$) and significant limitations in both central (CO: −1.5 ± 0.5 L/min, $P < 0.001$; SV: −13 ± 3 mL, $P < 0.001$; mPAP/CO slope: +0.4 ± 0.4 mm Hg/L/min, $P = 0.016$) and peripheral Fick components (a-VO2diff: −1.9 ± 0.6 mL/dL, $P < 0.001$, hemoglobin: −0.8 ± 0.3 g/dL, $P < 0.001$) compared to men with a positive HFpEF score. Oxygen delivery remained significantly lower in females with a positive HFpEF score even when indexed for body size (cardiac index −0.3 ± 0.2 L/min/m2, $P = 0.009$, and indexed SV −3 ± 2 mL/m2, $P = 0.002$). Despite having similar if not higher LV ejection fraction at rest and peak exercise, females with a positive HFpEF score had a smaller LVEDV and mass, even when corrected for body size, and a higher ratio of left atrial to LV volume than males with a positive HFpEF score. The elevated mPAP/CO slope was unlikely to be due to a difference in pulmonary vascular restistance, as this did not coincide with meaningful differences in O2 saturation or ventilatory efficiency. Notably, women with a positive HFpEF score had the lowest values for peak VO2, CO, and O2 delivery from all groups (compared to females with a negative HFpEF score, and males with a positive or negative HFpEf score).

Violin Plots With Sex Differences in VO2 and its Determinants in 555 Patients With a Positive (H2FPEF ≥6 or HFA-PEFF ≥5) vs 1,381 With a Negative HFpEF Score

Oxygen uptake (VO2) (central), and the Fick components determining VO2: peak stroke volume (upper left), peak heart rate (upper right), hemoglobin (lower right), and peak oxygen extraction (a-vO2difference) (lower left) Females without HFpEF (according to the HFpEF scores) have a lower average peak VO2, stroke volume, oxygen extraction and hemoglobin than males with HFpEF, while their heart rate is higher. HFpEF = heart failure with preserved ejection fraction.

Table 3Sex Differences: Negative vs Positive HFpEF Scoresa	**Negative HFpEF Score**		**Positive HFpEF Score**	
	Females (n = 630, 46%)	**Males (n = 751, 54%)**	**Females (n = 321, 58%)**	**Males (n = 234, 42%)**
Age, y	61 ± 15	60 ± 15	73 ± 8	73 ± 9
Height, cm	164 ± 7	177 ± 8b	161 ± 6	173 ± 7b
Weight, kg	70 ± 14	84 ± 14b	72 ± 14	82 ± 14b
Body surface area, m2	1.8 ± 0.2	2.0 ± 0.2b	1.8 ± 0.2	2.0 ± 0.2b
Body mass index, kg/m	26 ± 5	27 ± 4b	28 ± 6	27 ± 4
Fat mass index (fat mass/body weight)	0.35 ± 0.08	0.27 ± 0.06b	0.38 ± 0.08	0.28 ± 0.06b
Atrial fibrillation	23 (3)	68 (9)b	123 (38)	110 (47)
Diabetes mellitus	65 (10)	99 (13)	44 (14)	39 (17)
Hypertension	213 (34)	263 (35)	215 (67)	165 (70)
NT-proBNP, ng/L	130 (50-170)	90 (25-130)b	310 (190-520)	350 (150-480)
Exercise capacity				
Respiratory exchange	1.10 ± 0.11	1.11 ±	1.08 ± 0.11	1.11 ±

Table 3Sex Differences: Negative vs Positive HFpEF Scoresa	**Negative HFpEF Score**		**Positive HFpEF Score**	
	Females (n = 630, 46%)	**Males (n = 751, 54%)**	**Females (n = 321, 58%)**	**Males (n = 234, 42%)**
ratio (RER)		0.11		0.10b
Load/weight, W/kg	1.3 ± 0.7	1.7 ± 0.9b	0.8 ± 0.4	1.1 ± 0.5b
Peak VO2, mL/kg/min	18.1 ± 7.8	22.2 ± 9.7b	13.1 ± 4.1	15.9 ± 5.5b
Peak VO2, (Wasserman), % pred	78 ± 23	73 ± 23b	68 ± 20	63 ± 20b
Peak VO2 (Gläser), % pred	81 ± 24	80 ± 23	69 ± 18	71 ± 21b
Cardiac morphology				
LA volume index, mL/m2	21 ± 8	21 ± 9	32 ± 14	33 ± 12
End-systolic LA/LV volume, %	143 ± 82	113 ± 64b	212 ± 122	183 ± 134b
LV end-diastolic volume index rest, mL/m2	47 ± 13	56 ± 16b	45 ± 13	55 ± 15b
LV mass index, g/m2	72 ± 20	85 ± 24b	87 ± 28	101 ± 28b
Relative wall thickness	0.41 (0.35-0.48)	0.43 (0.37-0.50)	0.46 (0.40-0.56)	0.46 (0.39-0.56)
Diastolic LV internal diameter, mm	43 ± 6	47 ± 7b	43 ± 6	47 ± 7b
RV end-diastolic area, cm2	16 ± 5	20 ± 6	16 ± 4	20 ± 5

Table 3Sex Differences: Negative vs Positive HFpEF Scoresa	**Negative HFpEF Score**		**Positive HFpEF Score**	
	Females (n = 630, 46%)	**Males (n = 751, 54%)**	**Females (n = 321, 58%)**	**Males (n = 234, 42%)**
Rest and exercise cardiac function				
LA booster function by LACI (mL/s/m/cm)	3.0 (2.1-4.1)	3.0 (2.0-4.3)	3.5 (2.3-5.3)	3.2 (2.2-5.0)
MAPSE rest, mm	9 ± 3	10 ± 3b	8 ± 3	9 ± 3b
MAPSE peak, mm	13 ± 3	15 ± 3b	11 ± 3	12 ± 3b
Arterial elastance rest (Ea), mm Hg/mL	2.0 ± 0.6	1.8 ± 0.5b	2.1 ± 0.6	1.8 ± 0.5b
E/e' rest	10 ± 3	9 ± 3b	16 ± 7	14 ± 6b
LV stiffness (E/e'/LVEDV), mL−1	0.13 ± 0.06	0.09 ± 0.04b	0.21 ± 0.12	0.15 ± 0.07b
E/e' intermediate exercise	10 ± 3	9 ± 2b	16 ± 6	15 ± 5
mPAP/CO slope, mm Hg/L/min	2.7 ± 1.7	2.5 ± 1.5b	4.3 ± 2.1	3.9 ± 1.7b
exTRV, m/s	3.3 ± 0.3	3.4 ± 0.4b	3.5 ± 0.3	3.6 ± 0.4
LV end-diastolic volume index peak	47 ± 13	56 ± 16b	46 ± 12	56 ± 17b
LV ejection fraction rest, %	63 ± 8	62 ± 8b	63 ± 8	62 ± 8b
LV ejection fraction peak, %	69 ± 10	69 ± 10	69 ± 11	67 ± 10b
Stroke volume index rest, mL/m2	37 ± 8	37 ± 10	37 ± 9	39 ± 11b
Stroke volume index	44 ± 9	47 ± 11b	43 ± 11	46 ± 11b

Table 3Sex Differences: Negative vs Positive HFpEF Scoresa	**Negative HFpEF Score**		**Positive HFpEF Score**	
	Females (n = 630, 46%)	**Males (n = 751, 54%)**	**Females (n = 321, 58%)**	**Males (n = 234, 42%)**
peak, mL/m2				
Stroke volume peak, mL	78 ± 17	94 ± 22b	77 ± 17	90 ± 20b
Heart rate peak, beats/min	134 ± 24	132 ± 23	111 ± 21	110 ± 22
Cardiac output peak, L/min	10.5 ± 3.0	12.4 ± 3.6b	8.5 ± 2.2	10.0 ± 2.9b
Cardiac index peak, L/min/m2	6.0 ± 1.7	6.2 ± 1.9b	4.8 ± 1.2	5.1 ± 1.5b
Heart rate reserve, %	71 ± 23	69 ± 22	54 ± 24	55 ± 25
Oxygen delivery, L/min	1.9 ± 0.6	2.4 ± 0.7b	1.4 ± 0.4	1.8 ± 0.6b
Noncardiac factors				
a-vO2Diff, mL/dL	11.6 ± 2.8	14.7 ± 4.0b	11.3 ± 3.6	13.2 ± 3.5b
a-vO2Diff/Hb	0.86 ± 0.21	1.02 ± 0.27b	0.88 ± 0.26	0.97 ± 0.30b
CO/VO2 slope	6.2 ± 2.1	5.2 ± 1.9b	5.9 ± 2.4	5.3 ± 2.3b
Mixed venous saturation, %	33 ± 16	21 ± 20b	31 ± 17	24 ± 16b
Hemoglobin, g/dL	13.4 ± 1.1	14.7 ± 1.5b	12.9 ± 1.4	13.7 ± 1.7b
Transferrin saturation, %	26 ± 9	30 ± 12b	24 ± 10	26 ± 11
Iron deficiency	202 (53)	130	147 (58)	62 (37)b

Table 3Sex Differences: Negative vs Positive HFpEF Scoresa	Negative HFpEF Score		Positive HFpEF Score	
	Females (n = 630, 46%)	Males (n = 751, 54%) (31)b	Females (n = 321, 58%)	Males (n = 234, 42%)
Ve/MVV	0.60 ± 17	0.60 ± 0.21	0.59 ± 0.21	0.61 ± 0.16
SpO2, %	98 (96-99)	97 (96-98)b	97 (96-98)	98 (95-98)

Values are mean ± SD, n (%), or median (IQR).

a-vO2Diff/Hb = arteriovenous difference in oxygen content corrected for hemoglobin; CO/VO2 slope = cardiac output/oxygen uptake slope; Ea = arterial elastance (0.9. systolic blood pressure ÷ stroke volume); E/e' = ratio of early diastolic blood flow (E) over septal annular velocity (e'); exTRV = maximal tricuspid regurgitation velocity during exercise; LA = left atrium; LACI = left atrial volumetric/mechanical coupling index = indexed max left atrial volume ÷ late diastolic mitral annular velocity', (mL/s/m/cm); LV = left ventricle; LVEDV = LV end-diastolic volume; MAPSE = mitral annular plane systolic excursion; mPAP/CO slope = mean pulmonary artery pressure over cardiac output slope; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; SpO2 = exercise saturation by pulse oximetry; VO2 = oxygen uptake.

a A positive HFpEF score was defined as a total HFA-PEFF score ≥5 or a H2FPEF ≥6. A negative HFpEF score was defined as a total HFA-PEFF score <5 or a H2FPEF <6.

b *P* values <0.05 for post hoc group comparison female vs male.

Sex differences in individuals with negative HFpEF scores

Patients with negative HFpEF scores were younger and, more frequently, men (**Table 3**). However, women with a negative HFpEF score exhibited lower peak VO2 (−4.3 ± 0.9 mL/kg/min, $P < 0.001$) (**Figure 2**), peak exercise

CO (−1.9 ± 0.4 L/min, $P < 0.001$), SV (−16 ± 2 mL, $P < 0.001$), hemoglobin (−1.3 ± 0.2 g/dL, $P < 0.001$), and a-vO2diff (−3.1 ± 0.4 mL/dL, $P < 0.001$), compared to men with negative HFpEF scores (**Figure 2**). The sex difference in mean peak VO2, whether absolute or bodyweight-indexed, was even larger at a lower HFpEF probability (according to the logistic H2FPEF score described in the **Supplemental Methods** and **Supplemental Figure 4**) ($P <$ 0.001 for interaction). Like those with a positive HFpEF score, women with negative HFpEF scores had smaller hearts (indexed lower LVEDV and LV mass) and higher resting LV stiffness, arterial elastance and mPAP/CO slope than men with a negative HFpEF score (**Table 3**) ($P < 0.05$ for all). Women with a negative HFpEF score also had significantly lower transferrin saturation and were more likely iron deficient (53% vs 31%, $P < 0.001$). Notably, despite being, on average, 12 years younger, women with negative HFpEF scores had a lower peak exercise SV (−12 ± 3 mL, $P < 0.001$), hemoglobin (−0.3 ± 0.25 g/dL, $P = 0.003$), and a-vO2diff (−1.6 ± 0.5 mL/dL, $P < 0.001$) than men with a positive HFpEF score (**Figure 2**). However, their peak heart rate was higher (+24 ± 3 beats, $P < 0.001$), resulting in a comparable O2 delivery and peak VO2 to men with a positive HFpEF score. Women with negative HFpEF scores had indexed SV (−1.6 ± 1.5 mL/m2) as low as men with a positive HFpEF score. However, when corrected for their 12 ± 2 kg lower body weight, their peak VO2 was 2.2 ± 1.0 mL/kg/min higher than men with a positive HFpEF score ($P < 0.001$).

Which fick components explain the sex difference in exercise capacity?

Age, sex, and all Fick variables were significant univariable predictors of exercise capacity (power-to-weight ratio). In a multivariable linear regression analysis predicting cycling power-to-weight ratio (W/kg), age and the following Fick components emerged as independent predictors of power-to-weight ratio (in descending order of importance): peak heart rate, a-vO2diff, and SV (standardized estimates: −0.211 [age] and 0.462; 0.382; 0.324). In contrast, arterial O2 saturation and, importantly, sex were not independent predictors of the power-to-weight ratio in this multivariable model (**Table 4**, **Supplemental Figure 5**). Furthermore, hemoglobin was weakly and even

negatively correlated with power-to-weight ratio in this model (standardized estimate −0.037). As male and female HR were similar, a-vO2diff and SV are the modifiable Fick components accounting for the sex difference in cycling power-to-weight ratio. Peak SV and a-vO2diff remained independent predictors of power-to-weight ratio even when correcting for HFpEF probability (either as a binary outcome or when considered as the logistic H2FPEF score described in the **Supplemental Methods**). Similar results were obtained when replacing SV by indexed SV as the independent variable, or by replacing power-to-weight ratio with peak VO2 as the dependent variable: SV and a-vO2diff consistently explained the sex difference in exercise capacity. HFpEF score (positive or negative) was not a significant, independent predictor of peak VO2 or power-to-weight ratio in the multivariable model (standardized estimate: 0.04, *P* = 0.22). Collinearity between SV with a-vO2diff was acceptable (variance inflation factor: 1.53 and 1.54) both in the model predicting VO2 and power-to-weight ratio.

Table 4Multivariable Linear Regression for Predicting Cycling Power-to-Weight Ratio by Fick Components Adjusted for Age and Sex	**Estimate**	**SE**	***P* Value**	**Stand. Estimate**
Age	−0.01140	0.00112	1.79e0-23	−0.2112
O2 saturation	−0.00372	0.00453	0.4117	−0.0129
Hemoglobin (g/dL)	−0.01872	0.00887	0.0351	−0.0367
Heart rate peak	0.01426	6.07e-4	2.17e-103	0.4624
Stroke volume peak	0.01278	7.18e-4	4.33e0-64	0.3236
Oxygen extraction peak	0.07711	0.00385	1.01e0-78	0.3817

Table 4Multivariable Linear Regression for Predicting Cycling Power-to-Weight Ratio by Fick Components Adjusted for Age and Sex	**Estimate**	**SE**	***P* Value**	**Stand. Estimate**
Female–male	0.01531	0.03087	0.6199	0.0196

Discussion

To our knowledge, this is the largest cohort study investigating sex differences in peak VO2 and its Fick principle determinants among patients with unexplained dyspnea undergoing evaluation for HFpEF. The study found that women exhibited lower peak VO2 due to both reduced O2 delivery and extraction than men. Women displayed these oxygen cascade differences regardless whether their HFpEF scores were positive or negative. Women had lower peak exercise O2 delivery primarily due to a blunted peak exercise SV, which was associated with smaller, stiffer hearts, and greater afterload. This highlights an important contribution of female physiology to the greater functional limitations in women with unexplained dyspnea undergoing evaluation for HFpEF.

Few studies have examined sex differences in peak VO2 and its determinants in individuals with unexplained dyspnea with or without HFpEF.**8**,**9**,**11**,**12**,**17**,**21**,**23** We confirmed previous findings, demonstrating that females with a positive HFpEF score have smaller stiffer hearts, higher afterload, and lower peak VO2, CO, SV, hemoglobin, and a-vO2diff compared to males with HFpEF. Our study expands these findings by using a noninvasive, clinically feasible approach with assessments performed in the semi-supine posture (as opposed to supine measures performed in several previous invasive studies).**11**,**24** Additionally, we observed similar sex differences in the O2 pathway of individuals with unexplained dyspnea not fulfilling noninvasive diagnostic HFpEF criteria. Notably, women also had more often iron deficiency, possibly contributing to their lower a-vO2diff.

This provides important context, by highlighting that the greater functional limitation reported in women with HFpEF may be primarily a result of sex-related physiological differences that precede the development of overt HFpEF, that combine in an additive way to the HFpEF specific contributions to reduced peak VO2. Indeed, the relationship between HFpEF probability and peak VO2 is shifted downward and to the left in women (**Supplemental Figure 4**): Women have a lower exercise capacity for a given HFpEF probability threshold and they cross a given peak VO2 threshold at a lower HFpEF likelihood.

In addition to functional limitations, our results suggest there may be some sex-related factors that also contribute to greater burden of HFpEF-like features in women. A critical observation was that compared to men, women with or without a positive HFpEF score had smaller hearts—measured as lower LVEDV and LV mass, adjusted for body size, with the worst values seen in women with a positive HFpEF score. This finding aligns with a previous study, showing that women consistently exhibit smaller ventricular volumes and mass throughout adulthood.**25** However, there is growing recognition that these differences in LVEDV contribute to decreased exercise tolerance and an increased risk of HFpEF in women.**26**,**27** Resting and exercise cardiac magnetic resonance imaging studies have shown a strong association between resting LVEDV and peak VO2 in ostensibly healthy middle-aged women, with individuals in the smallest LVEDV quartile exhibiting the smallest resting and peak exercise SV and CO, with limited ability to decrease LV end-systolic volume during exercise.**26** Additionally, in patients with HFpEF, those with smaller resting LVEDV and higher ejection fraction—mostly women—had increased LV diastolic stiffness.**28** Our observations of a higher mPAP/CO slope and decreased peak CO (in the absence of differences in pulmonary vascular resistance) in women regardless of HFpEF scores are consistent with these previous findings, suggesting that the smaller female heart is stiffer and exhibits decreased capacity to augment CO during exercise, contributing to lower O2 transport and peak VO2. Notably, the lower hemoglobin concentration in

women was also an important contributor to their decreased O2 delivery. Therefore, addressing the lower hemoglobin (and related factors such as iron deficiency) may be a more feasible strategy to address much of the sex-related deficit in O2 delivery and peak VO2 than trying to improve the function of an aged, stiff cardiovascular system that has lost much of its plasticity.

There is also growing awareness of the importance of noncardiac factors to limitations in peak VO2 in both individuals with and without HFpEF. Indeed, Lau et al**8** reported noncardiac factors contribute to impaired exercise tolerance in female HFpEF patients, with peak exercise a-vO2diff being 14% lower in female patients than in males. We confirm and extend this finding by demonstrating that compared to men, women have a significantly lower a-vO2diff due to the combination of a lower CaO2 (secondary to lower hemoglobin) and also a lower DmO2, representing the transport of O2 from microvasculature to skeletal muscle mitochondria (**Figure 1**). Solely increasing convective O2 delivery up to the value seen in men would increase peak VO2 to a lower extent compared to what would occur by increasing DmO2 without altering O2 delivery (**Figure 1**). The mechanisms underlying the lower DmO2 in women remain uncertain; however, they may result from a decreased capillary-to-fiber ratio and mitochondrial oxidative capacity shown by reduced aerobic enzyme activity.**29** Therefore, targeting skeletal muscle microvasculature and mitochondria with therapies such as exercise training may be a crucial therapeutic target to improve peak VO2 in women at risk for or with HFpEF.**30** Whether emerging HFpEF therapies such as glucagon-like peptide 1 agonists and sodium glucose cotransporter protein 2 inhibitors can also influence these factors is also an intriguing question.**31**

Clinical implications

Exercise deficiency or a blunted response to exercise training in women throughout the lifespan may explain their cardiac and noncardiac impairments, emphasizing the need for exercise programs tailored to and

focused on enrolling women with or at risk for HFpEF. Indeed, exercise training is one of the few therapies that has established beneficial effects on the peripheral components of the O2 cascade in individuals with HFpEF.**32**,**33** Alternatively, current diagnostic and therapeutic strategies do not adequately address the key variables differentiating men and women either at risk for or with probable HFpEF, highlighting the value of additional phenotypic information provided by diagnostic approaches used in this study. Considering the involvement of central and peripheral steps in the O2 cascade, future interventions targeting exercise limitation in women should aim to improve both O2 delivery and utilization.

Study Limitations

Aside from the inherent limitations and biases of an observational single-center study, invasive hemodynamic measures of filling pressures and hemodynamics at rest and exercise were not included. However, our large study cohort represents the patient population and diagnostic work-up encountered in daily clinical practice. Likewise, DmO2, arterial elastance, and LV stiffness were estimated noninvasively, and therefore simplifications of their invasive counterparts. The assumptions made by the noninvasive methods are, however, less a limitation when evaluating group differences than absolute values. Moreover, all sex differences unveiled noninvasively in the HFpEF group concur with the findings from smaller invasive HFpEF cohorts,**8**,**9**,**11** supporting the validity of the differences identified in the group with negative HFpEF scores. Finally, a relatively modest proportion of our cohort met the criteria for a positive HFpEF score (28% of the total cohort). However, due to the total size of our cohort, this still represents one of the largest studies of individuals with HFpEF that includes detailed measurement of the O2 cascade.

Conclusions

Women with unexplained dyspnea displayed lower exercise tolerance related to central and peripheral deficits in their O2 cascade, regardless of HFpEF

likelihood based on diagnostic scores. Smaller ventricular size, increased LV-arterial stiffness, and compromised peripheral vascular-muscle function together may contribute to the vulnerability of women to develop HFpEF and exercise limitations.

14.Sex-Related Determinants of Exercise Intolerance in HFpEF: Not Just a Matter of the Heart!*

Heart failure (HF) with preserved left ventricular ejection fraction (HFpEF) is quickly becoming the most prevalent phenotype of HF**1** and is one of the most significant unmet needs in contemporary medicine.**2** Indeed, HFpEF presents physicians with several arduous challenges, including remarkable difficulties in accurate diagnosis and a scarce response to current medical therapy, with few exceptions.**2**,**3** As the outcomes of these patients remain relatively poor,**1** deeper insight into the ill-defined mechanisms subtending the development and progression of HFpEF would be crucial to implementing new therapeutic strategies. The "traditional" HFpEF phenotype is characterized by the association with female sex, older age, and several traditional cardiovascular risk factors and comorbidities, such as arterial hypertension, diabetes mellitus, dyslipidemia, visceral obesity, pulmonary disease, and chronic kidney disease. However, multiple diverse pathophysiologic derangements seem to delineate different HFpEF subphenotypes, including impaired systolic and diastolic function (especially during exercise), atrial dysfunction, abnormal autonomic tone, and alterations in peripheral mechanisms such as endothelial and skeletal muscle function.**4-7**

In recent years, the question of whether biological sex may represent a novel key in the pathophysiology of HFpEF has gained remarkable attention in the research setting**8-11**; indeed, the heterogeneity observed in HFpEF could partially depend on sex-related differences in the regulation of cardiovascular and metabolic processes**12**,**13** (**Figure 1**). Verwerft et al**14**, in this issue of *JACC: Advances*, address such a topic in the present issue of this journal, analyzing the determinants of functional capacity in a large

population of patients undergoing cardiopulmonary exercise testing with simultaneous exercise-stress echocardiography for unexplained dyspnea. The likelihood of HFpEF for each patient was assessed with either the H2FPEF or HFA-PEFF score.**15**,**16** Females and males were compared in the total population and according to HFpEF likelihood (ie, positive vs negative HFpEF scores). As a curious finding, there was a relatively low prevalence of typical comorbidities of HFpEF (ie, arterial hypertension, diabetes mellitus, and atrial fibrillation) in the general population.**14** However, probability scores might have limited sensitivity, especially in early disease stages**17**; exercise testing is often useful to refine the diagnostic work-up of suspected HFpEF,**18** and was appropriately used in the research protocol for patients evaluated with HFA-PEFF score. HFpEF was defined as likely in 29% (n = 555) of patients based on a positive HFA-PEFF or H2FPEF score, with a significantly higher prevalence in females (34%, n = 321) than males (24%, n = 234). Unfortunately, invasive hemodynamic evaluation at rest and exercise was not available to confirm the diagnosis of HFpEF, nor were alternative diagnoses formulated for patients with a low HFpEF probability.**14**

Regardless of HFpEF likelihood, peak oxygen consumption (VO2) was systematically lower in women than men, resulting from both reduced estimated oxygen delivery—due to smaller peak stroke volume (even when indexed for body surface area) and hemoglobin levels—and reduced arteriovenous oxygen difference (AVO2diff).**14** To our knowledge, previous invasive and noninvasive studies in patients with HFpEF had found no significant sex-related difference after indexing stroke volume to body surface area, neither at rest nor peak exercise.**10**,**19** Thus, the observed abnormality in the central component of VO2 (*ie*, cardiac systolic function) in women compared to men should be further investigated. On the other hand, the increase in estimated left ventricular stiffness reported in women, indicating more advanced diastolic dysfunction, is in keeping with the existing literature.**10** Another notable finding is that women also display a peripheral oxygen extraction (AVO2diff) impairment, which appears to be

mediated by lower estimated arterial oxygen content and lower estimated muscle diffusive oxygen conductance. Defects in oxygen uptake and utilization are key determinants of effort intolerance in HFpEF,**20** but no solid data about sex-dependent differences in such mechanisms are available. Partially limited by the non-invasive nature of their study, Verwerft and colleagues hypothesize that their results might be explained by decreased capillary density and mitochondrial oxidative capacity,**14** which, however, had been reported in older women and men equally.**21** Interestingly, iron deficiency was more prevalent in females,**14** and might further explain blunted oxygen utilization in this group.**22** Finally, the Authors found no significant differences in lung function between men and women regardless of HFpEF probability; however, they only evaluated breathing reserve. Thus, the contribution of sex-dependent ventilatory abnormalities to the pathophysiology of HFpEF remains to be clearly elucidated.

In conclusion, the paper by Verwerft et al**14** adds to the growing evidence regarding the association between the female sex and peculiar alterations in both central and peripheral components of VO2 that may contribute to an increased risk of developing exercise intolerance and, ultimately, HFpEF. Confirming the nature and extent of such sex-dependent pathophysiologic differences could ultimately pave the way for truly personalized therapeutic approaches.

15.Pre-eclampsia, Placental Factors, and Offspring Congenital Heart Disease*

Congenital heart disease (CHD) impacts 0.8% of all pregnancies and is the most common birth defect. Understanding factors that may contribute to the development of CHD allows opportunities for potential early interventions to decrease CHD risk.

The fetal cardiovascular system forms early in embryogenesis and therefore is subjected to maternal factors longer than any other. There is increasing recognition that maternal conditions can be associated with the development of CHD in the fetus. Maternal conditions are wide-ranging and include socioeconomic factors to maternal health factors such as obesity, diabetes, and pre-eclampsia. In this issue of *JACC: Advances*, Katlaps et al**1** examine the complex relationship between maternal pre-eclampsia and offspring CHD in incidents and subsequent pregnancies.

While pre-eclampsia is diagnosed after 20 weeks gestation, long after fetal cardiac structures are formed, the pathophysiologic changes of pre-eclampsia begin early in gestation. Increased levels of both soluble endoglin and fms-like tyrosine kinase 1 relative to vasculogenic placental growth factor and vascular endothelial growth factor are thought to inhibit spiral artery remodeling at the placental interface.**2** Similar imbalances in these same biomarkers were recently observed in 31 fetuses with heart defects and 138 children before corrective surgery for heart defects.**3** Studies suggest that angiogenic factor imbalance is predominantly found in early- but not late-onset pre-eclampsia, supporting the notion that pre-eclampsia is heterogeneous, with early and late variants. Furthermore, offspring CHD is more strongly associated with early than late preeclampsia, reinforcing the possibility that these variants differ.**4**

The study by Katlaps et al**1** adds to our understanding of the placenta-cardiovascular axis. The investigators utilized a unique mother-infant pair database to understand more about the relationship between maternal pre-eclampsia and offspring CHD.**1** The investigators leveraged a database of women who delivered in California between 2000 and 2012, a large and diverse population. They confirmed the previously reported association between pre-eclampsia and offspring CHD. In addition, they showed that that a history of pre-eclampsia is associated with an increased risk of future fetal CHD and that a history of fetal CHD is associated with an increased risk of future pre-eclampsia. The use of low-dose aspirin is used to decrease the development of pre-eclampsia, particularly in the high-risk population.

As the authors also highlight, perhaps aspirin could similarly reduce the development of CHD in offspring.

This study hints at the underlying vasculogenic profile of patients with pre-eclampsia, and in the perhaps *not-so* independent cohort of patients who have fetuses with CHD.

16.Pregnant Patients With PH Have Higher Rate of Adverse Events

Investigators analyzed maternal outcomes among women with PH using data from the Nationwide Readmissions Database from January 1, 2016, to December 31, 2020. The population comprised women older than 18 years with a primary or secondary diagnosis related to pregnancy.

A 2-step approach was used to categorize PH into 5 World Health Organization (WHO) groups. The primary outcomes were maternal mortality and 30-day nonelective readmission rate. The cumulative incidence of adverse cardiovascular events and the most common causes of 30-day nonelective readmission also were assessed.

A total of 9,922,142 pregnant women were identified, of whom 3532 (0.036%) had PH. Group 1 PH accounted for 1833 (51.90%) cases, group 2 PH had 676 (19.14%) cases, group 3 PH had 604 (17.10%) cases, group 4 PH had 23 (0.65%) cases, group 5 PH had 98 (2.77%) cases, and multifactorial PH had 298 (8.44%) cases. The pregnant women with PH were significantly older (31.7±6.8 years) compared with those without PH (29.2±5.7 years; P <.001).

It is essential to recognize that pregnancy-induced hemodynamic changes may exacerbate the progression of pulmonary hypertension…

The crude rate of maternal mortality was 0.85% in women with PH vs 0.01% in women without PH (P <.001). Women with PH had a nonelective 30-day readmission rate of 10.44%, which was significantly greater compared with a rate of 2.30% in women without PH. Among the WHO subgroups, the

multifactorial PH group had the highest rate of readmission (20.45%), and group 4 PH had the lowest rate (4.55%).

Diseases of the circulatory system complicating the puerperium (8.1%) and hypertensive heart disease with heart failure (7.6%) were the most common causes of readmission among the women with PH. In the non-PH group, severe preeclampsia involving the puerperium (12.9%) was the most common cause of readmission.

Women with PH had an increased incidence of adverse cardiovascular events, with 533 events (15.09%) vs 22,704 events (0.23%) in women without PH (P <.001). Adverse cardiovascular events occurred most frequently in the multifactorial PH group (35.91%) and group 2 PH (29.59%).

Adverse obstetric events occurred in 853 women in the PH group (24.15%), compared with 906,122 women (9.14%) without PH (P <.001). All obstetric complications, including eclampsia, severe preeclampsia, and obstetric shock, had a higher prevalence in the PH cohort. Fetal adverse events also were more common in the PH group (10.84%) vs the non-PH group (5.82%; P <.001). Preterm labor and spontaneous abortion occurred more frequently in women with PH, but no significant differences occurred for intrauterine death (P =.087) and stillbirth (P =.126).

Limitations of this study include potential misclassification bias and the lack of details on medication use, disease severity, mode of delivery, neonatal complications, and hemodynamic profiling. Also, early out-of-hospital and late maternal mortality were not evaluated.

“It is essential to recognize that pregnancy-induced hemodynamic changes may exacerbate the progression of pulmonary hypertension, impacting variables such as volume status, pulmonary vascular resistance, venous return, and cardiac output,” the study authors wrote.

17.Multiple Arterial vs Single Arterial CABG: Sex-Related Differences in Outcomes

BACKGROUND AND AIMS

Uncertainty exists over whether multiple arterial grafting has a sex-related association with survival after coronary artery bypass grafting. This study aims to compare the long-term survival of using multiple arterial grafting vs. single arterial grafting in women and men undergoing coronary artery bypass grafting.

METHODS

The retrospective study used the Australian and New Zealand Society of Cardiothoracic Surgical Database with linkage to the National Death Index. Patients from 2001 to 2020 were identified. Sex-stratified, inverse probability weighted Cox proportional hazard model was used to facilitate survival comparisons. The primary outcome was all-cause mortality.

RESULTS

A total number of 54 275 adult patients receiving at least two grafts in primary isolated bypass operations were analysed. The entire study cohort consisted of 10 693 (19.7%) female patients and 29 711 (54.7%) multiple arterial grafting procedures. At a median (interquartile range) postoperative follow-up of 4.9 (2.3–8.4) years, mortality was significantly lower in male patients undergoing multiarterial than single arterial procedures (adjusted hazard ratio 0.82; 95% confidence interval 0.77–0.87; P < .001). The survival benefit was also significant for females (adjusted hazard ratio 0.83; 95% confidence interval 0.76–0.91; P < .001) at a median (interquartile range) follow-up of 5.2 (2.4–8.7) years. The interaction model from Cox regression suggested insignificant subgroup effect from sex (P = .08) on the observed survival advantage. The survival benefits associated with multiple arterial grafting were consistent across all sex-stratified subgroups except for female patients with left main coronary disease.

CONCLUSIONS

Compared to single arterial grafting, multiple arterial revascularization is associated with improved long-term survival for women as well as men.

18.Early-Onset Hypertension and Sex-Specific Residual Risk for CVD in Type 2 Diabetes

OBJECTIVE

To investigate whether the sex disparities in type 2 diabetes-associated cardiovascular disease (CVD) risks may be related to early-onset hypertension that could benefit from intensive blood pressure (BP) control.

RESEARCH DESIGN AND METHODS

We analyzed intensive versus standard BP control in relation to incident CVD events in women and men with type 2 diabetes, based on their age of hypertension diagnosis.

RESULTS

Among 3,792 adults with type 2 diabetes (49% women), multivariable-adjusted CVD risk was increased per decade earlier age at hypertension diagnosis (hazard ratio 1.11 [1.03-1.21], P = 0.006). Excess risk associated with early-diagnosed hypertension was attenuated in the presence of intensive versus standard antihypertensive therapy in women (P = 0.036) but not men (P = 0.76).

CONCLUSIONS

Women with type 2 diabetes and early-onset hypertension may represent a higher-risk subpopulation that not only contributes to the excess in diabetes-related CVD risk for women but may benefit from intensive BP control.

19.Are the PAD Interventions for Men Safe in Women?

Because women are underrepresented in clinical trials evaluating endovascular therapy with stent implantation and bypass surgery for symptomatic femoropopliteal peripheral artery disease (PAD),

interventionalists have scant clinical evidence on which approach is best for their female patients.

Now, a pooled analysis of data from the REVIVE study has shown that both procedures have similar outcomes in women and men, with endovascular therapy having an edge in some metrics.

"In patients with symptomatic PAD involving the femoropopliteal segment, endovascular therapy with stent implantation vs bypass surgery was associated with a similar rate of 2-year major adverse limb events and amputation-free survival, but a lower rate of complications and significantly lower lengths of hospitalization, regardless of sex," Serdar Farhan, MD, assistant professor at the Icahn School of Medicine at Mount Sinai in New York City, reported here at the Society for Cardiovascular Angiography and Intervention (SCAI) 2024 Scientific Sessions.

"This pooled analysis of individual patient data further supports the efficacy and safety of endovascular therapy with stent implantation as an alternative to bypass surgery in both women and men," he said.

The analysis drew on individual patient data for 639 participants in the REVIVE study.

The data came from five randomized controlled trials comparing the two procedures; of the participants, 185 (29%) were women.

The goal, Farhan said, was to evaluate 2-year rates of major adverse limb events and other key outcomes such as amputation-free survival and primary patency. Shorter-term endpoints were 30-day complications related to a composite of bleeding, infection, and death as well as bleeding and infection as singular findings.

Where Are the Women in PAD Trials?

"Women are underrepresented in PAD revascularization trials and, so far, no robust data exist on sex-specific outcomes related to revascularization strategy," Farhan said when he presented the results. "The optimal

revascularization strategy for women with symptomatic PAD remains unknown, and the treatment recommendations are mainly based on clinical trial data, which predominantly enrolled men."

At 2 years, the rates of major adverse limb events with endovascular therapy and bypass surgery were not significantly different for the two sexes, at 40.6% and 42.1% (P = .764), respectively, in women and at 39.7% and 34.4% (P = .963), respectively, in men.

Rates of major adverse limb events, individual components of major adverse limb events, and primary patency were similar for the two procedures, regardless of sex. Endovascular therapy had significantly lower 30-day complication rates than did bypass surgery — 8.7% vs 25.9% (P = .002) in women and 5.9% vs 21.5% (P = .770) in men — along with significantly shorter hospital stays for both women (3.7 ± 5.7 vs 7.2 ± 4.2 days; P = .001) and men (2.8 ± 3.2 vs 7.4 ± 5.1 days; P = .001).

Farhan also reported 23 cases of technical failure in the endovascular arms — a rate of 2.9% (n = 3) for women and 9% (n = 20) for men — whereas none were reported in the bypass surgery arms.

Other key outcomes of endovascular therapy vs bypass surgery were:

- A composite of bleeding, infection, and death: 8.7% vs 25.9%, respectively, in women (P = .002) and 5.9% vs 21.5%, respectively, in men (P < .001)
- Bleeding: 5.8% vs 14.8%, respectively, in women (P = .04) and 4.5% vs 8.2%, respectively, in men (P < .11)
- Infection: 2.9% vs 16%, respectively, in women (P = .001) and 0.9% vs 15%, respectively, in men (P < .001)
- Death: 1% vs 0%, respectively, in women (P = NA) and 0.5% vs 0.4%, respectively, in men (P < .96).

"Ideally, this means an operator has the choice to offer two strategies to the patient that are similarly effective," Farhan explained after his presentation.

"Interestingly, we saw that the composite of bleeding, infections, or death within 30 days is significantly less with endovascular therapy in both sexes," he added, noting that the rate of bleeding in women who had endovascular therapy was one third the rate in those who had bypass surgery, whereas in men, the bleeding rate with endovascular therapy was half that of bypass.

"It means that there might be a signal toward a lower risk of bleeding in the early phase in women than in men when we apply endovascular therapy with stent implantation instead bypass surgery," Farhan added. "However, we need larger studies to validate this."

Call for Broader Studies

This pooled analysis of REVIVE data reinforces the efficacy and safety of endovascular therapy for PAD for both sexes, said Ethan Korngold, MD, chair of structural and interventional cardiology at Providence Health Institute in Portland, Oregon.

However, he added, future studies of endovascular therapy for PAD should broaden their scope.

"It's notable that this trial focused on patients treated with stents," Korngold said. "I would love to see future research focus on other techniques that we use to treat PAD, whether it's drug-coated balloons or atherectomy, just to encompass the full range of endovascular treatments, but it's very encouraging that both sexes benefited from it and both did very well."

That focus on one specific therapy is perhaps the study's primary limitation, he said. "But I think these are great data, and we need to be doing more of this type of research to see the patients that we're reaching and to see how they benefit from this," Korngold added.

20.2008 to 2021 Saw Increase in Prevalence of Chronic HTN in Pregnancy

For pregnant individuals, the prevalence of chronic hypertension more than doubled between 2008 and 2021, according to a study published online June 17 in Hypertension.

Stephanie A. Leonard, Ph.D., from the Stanford University School of Medicine in California, and colleagues analyzed commercial insurance claims from 2007 to 2021 and assessed the prevalence of chronic hypertension during pregnancy and trends in oral antihypertensive medication use.

The researchers found that between 2008 and 2021, the prevalence of chronic hypertension increased steadily from 1.8 to 3.7 percent among 1,900,196 pregnancies. During the study period, antihypertensive medication use among those with chronic hypertension was relatively stable (57 to 60 percent). There was a decrease seen in the proportion of pregnant individuals with chronic hypertension treated with methyldopa or hydrochlorothiazide (from 29 to 2 percent and from 11 to 5 percent, respectively), and there was an increase seen in the proportion treated with labetalol or nifedipine (from 19 to 42 percent and from 9 to 17 percent, respectively). Following the 2017 American College of Cardiology and American Heart Association hypertension guidelines, there was no change observed in the prevalence or treatment of chronic hypertension during pregnancy.

"There were large shifts in the medications used to treat chronic hypertension in pregnancy, with labetalol supplanting methyldopa as the most commonly used antihypertensive medication," the authors write.

21. Rate of CVD in Mid-Adulthood Increased for Women With Perinatal Depression

Women with perinatal depression (PND) have an elevated long-term risk for cardiovascular disease (CVD), according to a study published online June 18 in the European Heart Journal.

Donghao Lu, Ph.D., from the Karolinska Institutet in Stockholm, and colleagues conducted a nationwide population-based matched cohort study involving 55,539 women diagnosed with PND during 2001 to 2014 and 545,567 unaffected matched women to examine the long-term risk for CVD.

The researchers found that 6.4 and 3.7 percent of women with PND and unaffected women, respectively, developed CVD during the follow-up of up to 20 years. Women with PND had a significantly higher risk for developing CVD compared with matched unaffected women (adjusted hazard ratio, 1.36) and compared with their sisters (adjusted hazard ratio, 1.20). Women without a history of psychiatric disorder had the most pronounced results. The association was seen for all CVD subtypes, with the highest hazard ratios for hypertensive disease, ischemic heart disease, and heart failure (hazard ratios, 1.50, 1.37, and 1.36, respectively).

"Although familial factors may partly play a role here, our findings lend support to the ongoing discussion on factoring in reproductive history, including PND, for CVD risk assessment and prediction in women," the authors write.

22.In Late-Onset Hypertension, Men Have Worse Outcomes Than Women

Although hypertension is prevalent among women, they are underrepresented in hypertension trials. As such, data about late-onset hypertension outcomes among women are limited.

Investigators from the University of Ottawa and The Ottawa Hospital in Canada sourced data for this study from the Institute for Clinical Evaluative Sciences (ICES) database which collects data from more than 14 million

residents in Ontario, Canada. Patients (N=266,273) aged 66 years or older with incident hypertension between 2010 and 2017 were evaluated for a composite primary outcome through 2021 on the basis of gender. The primary composite outcome was defined as nonfatal ischemic stroke, nonfatal myocardial infarction, and congestive heart failure.

The study population comprised 51% women and 49% men and they had mean ages of 74 (SD, 7) and 74 (SD, 6) years (P =.02), 2.7% and 3.0% had chronic obstructive pulmonary disease (P =.02), 1.3% and 1.8% had chronic liver disease (P =.04), and 43.8% and 39.8% were not using any blood pressure-lowering medications (P <.001), respectively.

…female sex was protective against adverse cardiac outcome among older patients with hypertension.

During a median 6.6-year follow-up, the composite outcome occurred among 38,586 individuals and death occurred among 77,005 individuals, 45.7% of whom were women.

Women had a lower crude rate of (incidence rate [IR], 287.3 vs 311.7 per 1000 person-years [py]; P <.001) and lower risk for (adjusted hazard ratio [aHR], 0.75; 95% CI, 0.73-0.76) the composite outcome compared with men. Similarly, women had a lower crude mortality rate (IR, 238.4 vs 251.4 per 1000 py; P <.001) and were at lower risk of death (aHR, 0.72; 95% CI, 0.71-0.73) relative to men.

Similarly, women were at lower risk for cardiovascular death (aHR, 0.85; 95% CI, 0.82-0.99) and revascularization (aHR, 0.91; 95% CI, 0.89-0.94) than men.

In subgroup analyses, significant interactions were observed for diabetes (P <.01), prior cardiovascular diagnosis (P <.01), use of blood pressure lowering medications (P <.01), and year of index hospitalization (P =.01). In which, risk for the composite outcome was higher among women than men with diabetes than without (aHR, 0.82 vs 0.73), with prior cardiovascular

diagnoses than without (aHR, 0.91 vs 0.75), and with blood pressure medication use than without (aHR, 0.77 vs 0.68), respectively.

The major limitation of this study was that blood pressure data were not available.

"…we found that there are sex-specific differences in cardiovascular outcomes and death," the study authors concluded. "Importantly, and contrary to what has been observed among younger cohorts where females with hypertension are higher risk for cardiovascular events, female sex was protective against adverse cardiac outcome among older patients with hypertension in our current study."