News in September 2024

1. Prevalence of Frequent Premature Ventricular Contractions and Nonsustained Ventricular Tachycardia in Older Women Screened for Atrial Fibrillation

BACKGROUND

Frequent premature ventricular contractions (PVCs) and nonsustained ventricular tachycardia (NSVT) have been associated with cardiovascular disease and mortality. Their prevalence, especially in ambulatory populations, is understudied and limited by few female participants and the use of short-duration (24- to 48-hour) monitoring.

OBJECTIVE

The objective of this study was to report the prevalence of frequent PVCs and NSVT in a community-based population of women likely to undergo electrocardiogram (ECG) screening by sequential patch monitoring.

METHODS

Participants from the Women's Health Initiative Strong and Healthy (WHISH) trial with no history of atrial fibrillation (AF) but 5-year predicted risk of incident AF ≥5% by CHARGE-AF score were randomly selected to undergo screening with 7-day ECG patch monitors at baseline, 6 months, and 12 months. Recordings were reviewed for PVCs and NSVT (>5 beats); data were analyzed with multivariate regression models.

RESULTS

There were 1067 participants who underwent ECG screening at baseline, 866 at 6 months, and 777 at 12 months. Frequent PVCs were found on at least 1 patch from 4.3% of participants, and 1 or more episodes of NSVT were found in 12 (1.1%) women. PVC frequency directly correlated with CHARGE-AF score and NSVT on any patch. Detection of frequent PVCs increased with sequential monitoring.

CONCLUSION

In postmenopausal women at high risk for AF, frequent PVCs were relatively common (4.3%) and correlated with higher CHARGE-AF score. As strategies for AF screening continue to evolve, particularly in those individuals at high risk of AF, the prevalence of incidental ventricular arrhythmias is an important benchmark to guide clinical decision-making.

2. Superior effect of long-term community-based high-intensity interval training on cardiovascular and functional parameters in low-income older women

The physiological and behaviour changes that occur during aging result in reduced functional capacity, poor quality of life, and increased risk of non-communicable chronic diseases,1 whereas cardiovascular disease (CVD) is the most prevalent.2 Physical activity/exercise is a well-established tool to counteract age-related disorders, and to reduce incidence of CVD and mortality.1,2 However, the adherence to physical activity/exercise recommendations is very low, and women, older and low-income individuals, are among the least adherent.3 Community-based exercise programmes (CBEPs) (i.e. structured set of exercises designed for group of individuals, commonly with similar conditions, with the goal of promoting and continuing regular exercise in the community) may be an important strategy to overcome some barriers in these least adherent groups, because they require lower financial, human, and material resources than individualized programmes.4

Although CBEP have improved physical fitness and several health-related outcomes in older individuals,4 its long-term effects on important cardiovascular risk factors such as arterial stiffness and blood pressure (BP) are unknown. Given that the benefits of exercise to older individuals may be modulated by its intensity and modality,1,4 to investigate the benefits of different intensities/modalities of long-term CBEP in older individuals, mainly those least adherent, may help develop specific recommendations for promoting health. Therefore, the present prospective, randomized, and

single-blinded study investigated the effects of long-term (nine months) CBEP of different intensities/modalities, and their short-term (three months) interruption on anthropometric, cardiovascular, and functional parameters in low-income older women.

3. Menopausal Transition Linked to Adverse Changes in Lipoprotein Profile

Menopausal status is associated with adverse changes in lipoprotein profiles, according to a study presented at the European Society of Cardiology Congress 2024, held from Aug. 30 to Sept. 2 in London.

Stephanie Moreno, M.D., from the University of Texas Southwestern in Dallas, and colleagues examined changes in lipid measures through the menopause transition using data from the Dallas Heart Study (DHS). Women with known menopausal status who underwent nuclear magnetic resonance LipoProfile lipid platform analysis at DHS-I and DHS-II were included. Data were analyzed for 440 premenopausal women, 298 perimenopausal women, 508 postmenopausal women, and 1,364 men.

The researchers found that women experienced a greater change in low-density lipoprotein (LDL) particles from DHS-I to DHS-II compared with men; premenopausal and perimenopausal women had the greatest change. Compared with men, postmenopausal women had a greater reduction in high-density lipoprotein (HDL) particles between DHS-I and DHS-II. Greater change in small-dense LDL was seen for women versus men, with the most pronounced changes in perimenopausal women. Significantly greater reductions in large HDL were seen in perimenopausal and postmenopausal women compared with men; no difference was seen in the change in large HDL between premenopausal women and men.

"We found that menopause is associated with adverse changes in lipoprotein profiles, with the most pronounced changes found to be in increases in 'bad' LDL-particles and subfractions observed for perimenopausal women," Moreno said in a statement. "When looked at together, these changes could help

explain the increase of cardiovascular disease in postmenopausal women and help determine if earlier interventions are warranted."

4. Association Between Menopausal Vasomotor Symptoms and Subclinical ASCVD

BACKGROUND

Menopausal vasomotor symptoms (VMS) are increasingly emphasized as a potentially important cardiovascular risk factor, but their role is still unclear. We assessed the association between VMS and subclinical atherosclerotic cardiovascular disease in peri- and postmenopausal women.

METHODS AND RESULTS

Using a cross-sectional study design, questionnaire data were collected from a population-based sample of women aged 50 to 64. The questionnaire asked whether menopause was/is associated with bothersome VMS. A 4-point severity scale was used: (1) never, (2) mild, (3) moderate, and (4) severe. The VMS duration and time of onset were also assessed. Associations with subclinical atherosclerotic cardiovascular disease, detected via coronary computed tomography angiography, coronary artery calcium score, and carotid ultrasound were assessed using the outcome variables "any coronary atherosclerosis," "segmental involvement score >3," "coronary artery calcium score >100," and "any carotid plaque," using logistic regression. Covariate adjustments included socioeconomic, lifestyle, and clinical factors. Of 2995 women, 14.2% reported ever severe, 18.1% ever moderate, and 67.7% ever mild/never VMS. Using the latter as reference, ever severe VMS were significantly associated with coronary computed tomography angiography-detected coronary atherosclerosis (multivariable adjusted odds ratio, 1.33 [95% CI, 1.02-1.72]). Corresponding results for ever severe VMS persisting >5 years or beginning before the final menstrual period were 1.50 (95% CI, 1.07-2.11) and 1.66 (95% CI, 1.10-2.50), respectively. No significant association was observed with segmental involvement score >3, coronary artery calcium score >100, or with any carotid plaque.

CONCLUSIONS

Ever occurring severe, but not moderate, VMS were significantly associated with subclinical coronary computed tomography angiography-detected atherosclerosis, independent of a broad range of cardiovascular risk factors and especially in case of long durations or early onset.

5. Inflammation, Cholesterol, Lp(a) Levels, and 30-Year Cardiovascular Outcomes in Women

Modifiable blood biomarkers such as hsCRP, LDL-C, and Lp(a) can be instrumental for understanding biology, predicting risk, and targeting cardiovascular interventions. However, data are scarce on the long term (25- to 30-year) risks associated with these biomarkers when used alone and in combination, particularly among women for whom cardiovascular disease remains under-diagnosed and under-treated.

My colleagues and I hypothesized that a single baseline measure of hsCRP, LDL-C, and Lp(a) obtained in mid-life could predict future cardiovascular risk in women over a 30-year period. We addressed these issues in the NIH-funded Women's Health Study (WHS), a prospective cohort of 27,939 initially healthy American women who had all three biomarkers measured in a blood sample obtained at baseline and who have been followed for over a 30-year period for major cardiovascular events.

Our results are striking. First, low grade systemic inflammation detected by hsCRP was a stronger predictor of future cardiovascular events over the next 30 years than either LDL-C or Lp(a), yet in clinical practice hsCRP is the least likely biomarker to be measured by most clinicians. These data should challenge internists to learn more about inflammation biology, particularly as low-dose colchicine has now been approved by the US FDA as the first targeted anti-inflammatory drug to prevent atherosclerotic events.

Second, hsCRP, LDL-C, and Lp(a) are independent of each other and tell us that different biologic processes are at play for individual patients; we therefore should be targeting preventive efforts at the biologic issue our

individual patient suffers from and not assume one size fits all. Some women will be affected by more than one of these abnormal pathways – when used in combination, those who had elevated levels of all three biomarkers had a threefold elevation of risk, even when only 40 years old.

Last, we need to move well past 5-year or 10-year risk predictions. If one calculates cardiovascular risk in the manner suggested by current guidelines, very few women will be identified as being at high risk until they are well into their 60s if not 70s, too late for real prevention. A new way to address prevention is needed, and a simple one-time screen early in life for hsCRP, LDL-C, and Lp(a) will get us a long way toward that goal.

The bottom line is that doctors cannot treat what they do not measure, and prevention cannot wait until advance disease is present.

6. Hypertensive Disorders of Pregnancy and Brain Health in Midlife: The CARDIA Study

BACKGROUND:

To understand the role of hypertensive disorders of pregnancy (HDP), including preeclampsia and gestational hypertension (GH), in brain health earlier in life, we investigated the association of HDP with midlife cognition and brain health.

METHODS:

We studied a prospective cohort of women, baseline age 18 to 30 years, who were assessed at study years 25 and 30 with a cognitive battery and a subset with brain magnetic resonance imaging. A history of HDP was defined based on self-report. We conducted linear regression to assess the association of a history of preeclampsia, GH, or no HDP with cognition and brain magnetic resonance imaging white matter hyperintensities.

RESULTS:

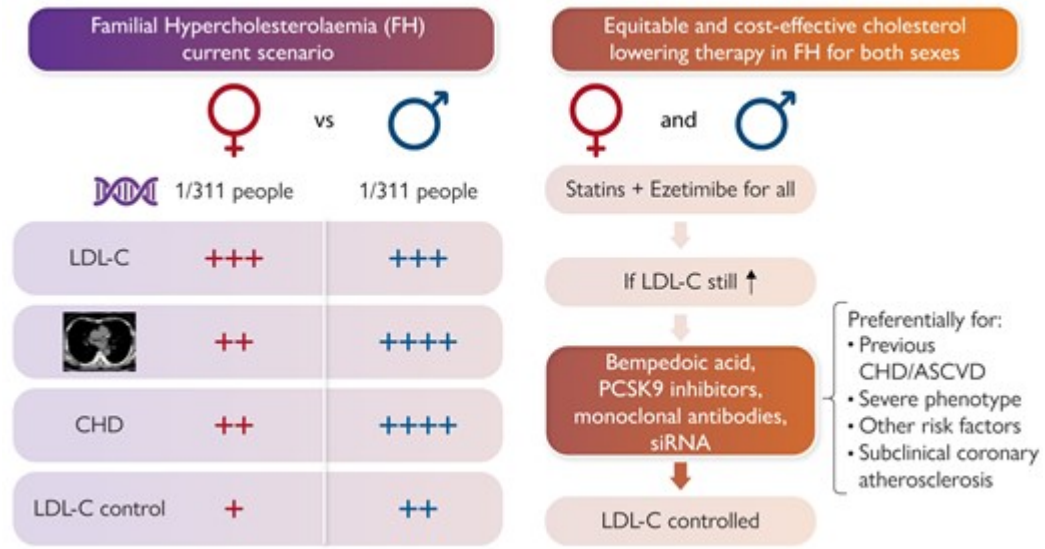
Among 1441 women (mean age, 55.2±3.6 years), 202 reported preeclampsia and 112 reported GH. GH was associated with worse cognitive performance: global cognition (mean score, 23.2 versus 24.0; P=0.018), processing speed (67.5 versus 71.3; P=0.01), verbal fluency (29.5 versus 31.1; P=0.033), and a

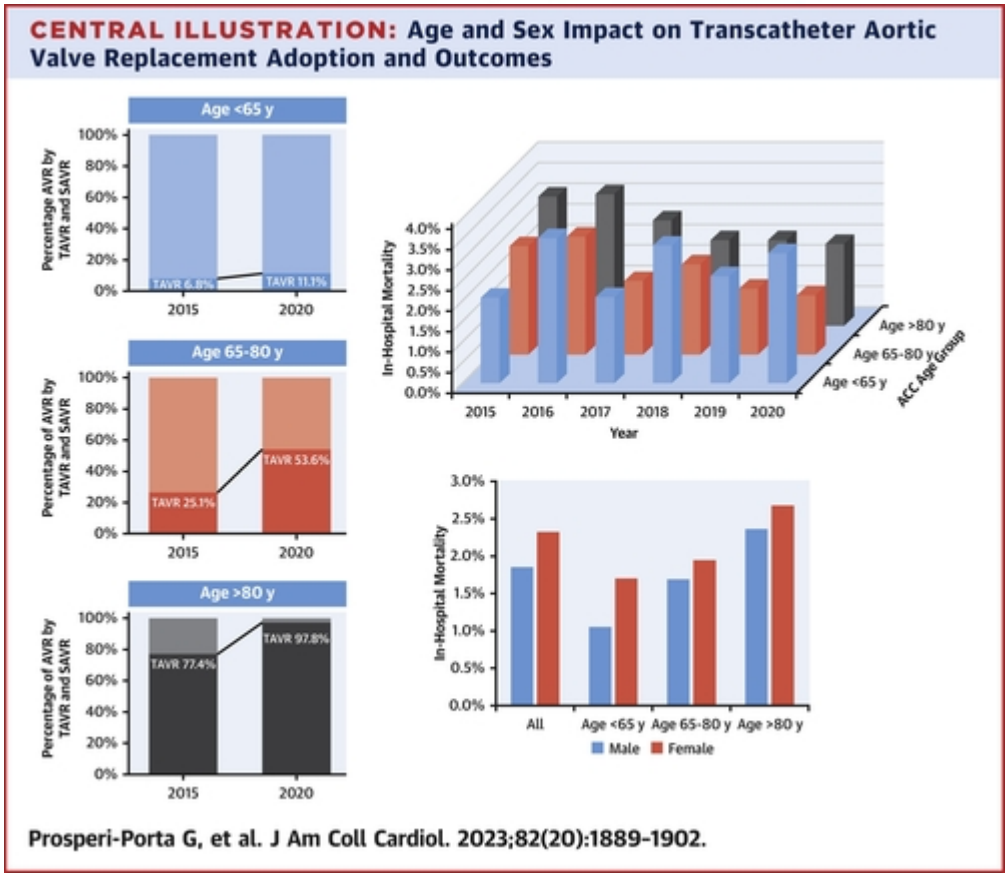
trend for executive function (24.3 versus 22.6; P=0.09), after multivariable adjustment. GH was associated with a greater 5-year decline in processing speed (mean change, −4.9 versus −2.7; P=0.049) and executive function (−1.7 versus 0.3; P=0.047); preeclampsia was associated with a greater 5-year decline on delayed verbal memory (−0.3 versus 0.1; P=0.041). GH and preeclampsia were associated with greater white matter hyperintensities in the parietal and frontal lobes, respectively.

CONCLUSIONS:

GH and preeclampsia are associated with cognition and white matter hyperintensities during midlife, with differences in cognitive domains and brain lobes. Women with HDP may need to be closely monitored for adverse brain outcomes starting in midlife.

7. Familial hypercholesterolaemia: need for equitable treatment in women and men





The current situation of subclinical coronary atherosclerosis, CHD, and cholesterol control in women and men with FH.1,10,13 Proposal for equitable and cost-effective LDL-C lowering in FH for both sexes. ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; FH,

familial hypercholesterolaemia; LDL-C, LDL-cholesterol; PCSK9; proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA.

8. Sex differences in treatment of familial hypercholesterolaemia: a meta-analysis

Introduction

Familial hypercholesterolaemia (FH) is a highly prevalent monogenic disorder characterized by lifelong elevated blood levels of LDL cholesterol (LDL-C). Its worldwide prevalence is 1/311 with an estimated 25–30 million people affected globally.1 Left untreated, it leads to premature atherosclerotic cardiovascular disease (ASCVD), particularly coronary artery disease (CAD), in addition to greater medical costs and a reduced health-related quality of life.2–4 Prompt recognition and treatment with statins and other lipid-lowering therapies (LLTs) is highly efficacious and can normalize life expectancy.

Despite this, FH remains under-recognized and under-treated worldwide. The reasons for under-treatment remain incompletely understood, and there is limited information on barriers to care in FH. As an autosomal semi-dominant trait, FH affects males and females equally. Yet, there is growing recognition that sex may play a role in the clinical presentation and management of this illness, contributing to barriers to care. Increasing reports from our groups and others suggest that female patients with FH may have an increased burden of LDL-C compared with males, are diagnosed later, treated less aggressively with guideline-mandated medical therapies, and are less likely to reach recommended LDL-C targets or thresholds.5–8 These treatment differences were observed in both adults and children from the Familial Hypercholesterolaemia Studies Collaboration (FHSC), the largest global registry of patients with FH worldwide.6,9 Furthermore, whether sex is an independent predictor of outcomes in FH remains debated. While some studies have demonstrated greater ASCVD in males,6 others have shown no difference or greater risk in

females.10–12 The FHSC reported that in 42 167 patients from 56 countries (53.6% females) the prevalence of CAD (17.4%), increasing with untreated LDL-C levels, was two times lower in females than in males, and the overall ASCVD risk was lower in index and non-index females.6 Despite this, females with FH are at greater risk of CAD mortality than non-FH females. Additionally, the same FH diagnostic criteria are used for both males and females, without consideration of variability of LDL-C levels by sex throughout life, especially during pregnancy and in post-menopausal years.

In order to better understand the scope and extent of this question, we aimed to characterize sex-related disparities in management and ASCVD in patients with FH. To address this, we conducted a systematic review and meta-analysis of studies examining the associations between sex and treatment, response, achieved LDL-C levels, and guideline-recommended targets in FH, both in clinical trials to detect whether response to fixed doses of LLT differs between sexes and in real-world observational data from registries and cohort studies. Associations between sex and cardiovascular disease (CVD) risk among patients with FH were subsequently investigated.

Methods

Protocol and registration

This systematic review study was registered in the PROSPERO prospective database for systematic reviews (CRD42022353297) and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA),13 Meta-analysis Of Observational Studies in Epidemiology (MOOSE),14 and Sex and Gender Equity in Research (SAGER)15 consensus statements.

Information sources and search strategy

Search strategies were developed and executed with the assistance of a medical librarian (L.H.) with expertise supporting systematic reviews. Database searches were completed for MEDLINE, Embase, The Cochrane

library, PubMed, Scopus, and PsycInfo. Clinical trial registries including ClinicalTrials.gov, the International Clinical Trials Registry Platform, UK Clinical Trials Gateway, and the ProQuest Dissertations and Theses database were also searched. Grey literature was sourced from Google Scholar and Open Grey. Reference lists of relevant systematic reviews were also searched for additional citations. No language limits were applied. Searches were conducted from database inception to 21 July 2020; the Medline search was rerun prior to manuscript preparation in 26 April 2023. A complete description of the search strategy is provided in the Supplementary data online, Appendices. The authors acknowledge that while 'female' or 'male' refer to an individual's biological sex and 'woman' or 'man' refer to an individual's gender, historically these terms have been used interchangeable in the literature; all these terms were included in the search strategy. However, in the present study the terms 'female' or 'male' are used for consistency as it pertains to biological sex.

Study selection and eligibility criteria

Candidate titles, abstracts, and full-text articles were evaluated in duplicate by five independent reviewers (A.G., J.G., I.I., I.R., L.E.A.) using Rayyan systematic review software (www.rayyan.ai). Disagreements were resolved by discussion to consensus. Studies were considered eligible for inclusion if they: (i) were interventional and/or observational studies in adult participants (age ≥18 years) with heterozygous FH (diagnosed using genetic and/or common clinical criteria) and (ii) reported data separately for male and female participants on our outcomes of interest, as described below. Non-human studies, case reports, editorials, conference abstracts, and narrative reviews were excluded. Any clinical definition of FH used in studies was accepted.

Outcomes

Our primary outcome consisted of the number of females vs. males treated with any LLTs in the included studies. Treatment with specific drug classes

where studies reported them [statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors] was also examined. The secondary outcomes consisted of: (i) absolute and relative reductions in LDL-C experienced by male and female patients with FH treated with LLTs and (ii) attainment of guideline-recommended LDL-C reduction targets in these patients (defined as ≥50% reductions in LDL-C from baseline, LDL-C < 2.5 mmol/L, LDL-C < 1.8 mmol/L). Sex-specific differences in fatal and non-fatal major adverse cardiovascular events (MACE) were examined afterwards.

Data extraction

Data were extracted from studies deemed to meet eligibility criteria by at least two independent reviewers (A.G., J.G., I.I., I.R., L.E.A.). These included details on general study characteristics (first author, design, recruitment period, duration of follow-up); information about the studied population (mean age, number and proportion of males and females, diagnostic and treatment characteristics); and information on the outcomes in the study. Characteristics of studies were summarized in tabular format and narratively synthesized. Unadjusted and adjusted measures of relative risk and 95% confidence intervals (CIs) were also extracted. Maximally adjusted risk measure that was available from studies and risk estimates corresponding to the longest duration of follow-up were used. Study authors were not contacted for additional data. Quality of eligible studies was assessed using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for quantitative studies after assessing the following domains: selection bias, study design, confounders, blinding, data collection method, and withdrawals and dropouts.16 Generally, the global rating of a study was considered to be strong if none of the quality domains were rated as weak; moderate if one domain was rated as weak; and weak if two or more domains were rated as weak.

Statistical analyses

Meta-analyses were conducted using inverse-variance models incorporating random effects estimated using the method of DerSimonian and Laird.17 For dichotomous outcomes, pooled estimates of effect size were calculated as odds ratios (OR) with 95% CIs. Weighted mean differences were calculated for continuous outcomes. Summary estimates were displayed graphically with forest plots. Heterogeneity was assessed using the $I2$ statistic; heterogeneity was interpreted using the following thresholds: 0%–40%: might not be important; 30%–60%: may represent moderate heterogeneity; 50%–90%: may represent substantial heterogeneity; and 75%–100%: considerable heterogeneity. Publication bias was assessed visually using funnel plots, and where analyses included >10 studies, formally using Egger's weighted regression and significance set at $P < .10$.18 If publication bias was present, we used the trim-and-fill method to control for publication bias. This technique may not be entirely suitable when excess heterogeneity is present,19 and we therefore also reported heterogeneity using the $I2$ statistic (see Limitations). Sources of heterogeneity in our primary outcome were investigated through subgroup analyses and meta-regression. Subgroups were stratified by: year of publication (set at before and after 2016 to represent the introduction of ICD-10 codes for FH), FH diagnosis criteria (majority (>50%) with genetic testing, 100% with clinical criteria, combination of minority (<50%) with genetic testing and remaining with clinical criteria, and 100% using LDL-C cut-offs), study sample size (fewer or more than 1000 participants), and World Health Organization (WHO) geographical location (Americas, Europe, Western Pacific, and International). x2 statistical test was used to detect differences between subgroups. Univariate meta-regression was performed to explore potential sources of heterogeneity using the following covariates: year of publication, age of participants, proportion of females in included studies, mean LDL-C reduction, and the proportion of individuals with CVD. One study included in the analyses sourced data from multiple national registries,6 creating the potential for overlap with multiple cohorts; accordingly, additional sensitivity analyses in which this study was excluded were conducted. Meta-regressions were conducted using a mixed-effects

approach to account for between- and within-study heterogeneity, with restricted maximum likelihood estimation of between-study variance. For subgroup and meta-regression analyses, two-sided *P*-values <.05 were considered significant. Additional details of our analyses are described in the Supplementary data online, *Appendix*. Analyses were performed in Review Manager 5.4 and RStudio (version 2023.03.0 + 386).

Results

Database searches identified 5601 records which were reduced to 4432 following duplicates removal. From initial abstract screening, 3836 studies were excluded, and a total of 596 full-text articles were reviewed. Of these, 133 studies met criteria for sex differences in the treatment of FH and were included in the qualitative analyses (*Figure 1*). These studies comprised 16 interventional clinical trials testing a lipid-lowering agent (eight randomized and eight non-randomized clinical trials), 36 observational studies presenting data on sex differences in FH treatment, and 81 observational studies on sex differences in CVD outcomes. Observational studies were prospective, retrospective, or cross-sectional cohort studies. Characteristics of all studies are shown in Supplementary data online, *Table S1*, while a risk of bias per study is presented in Supplementary data online, *Appendix S3*. When evaluated by the EPHPP tool, most clinical trials were rated as being moderate, while observational studies ranged from moderate to strong, with the greatest threats to validity being because of study design or blinding.

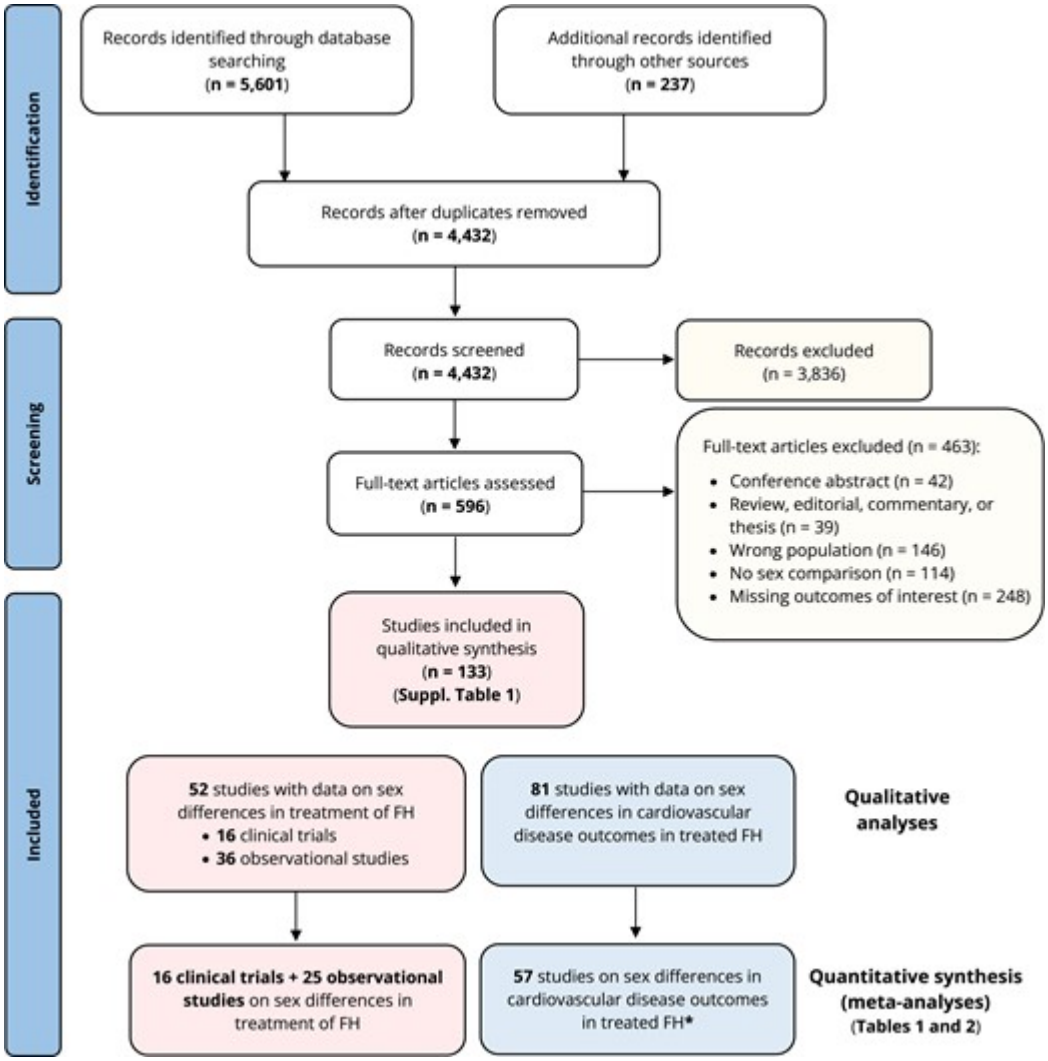


Figure 1

Preferred Reporting Items for Systematic reviews and Meta-Analyses flow chart of studies included in the systematic review of sex differences in the treatment of familial hypercholesterolaemia. *Seven studies were describing both data on sex differences in the treatment of familial hypercholesterolaemia and cardiovascular disease outcomes in patients with treated familial hypercholesterolaemia. FH, familial hypercholesterolaemia

There were 16 clinical trials of LLTs in which an analysis by sex was provided (1840 participants; 49.4% females). In 12 studies in which a mean percent LDL-C reduction value was available, there were no differences between males and females in response to fixed doses of LLTs (*Figure 2*),

suggesting that patient sex was a not a determinant of therapeutic response. Absolute LDL-C reductions in males and females from the reviewed clinical trials are reported in Supplementary data online, *Figure S1*, while mean LDL-C reductions from LLT are shown in Supplementary data online, *Figure S2*.

Figure 2

Mean LDL cholesterol percent reduction in clinical trials included in the systematic review. Asterisks denote studies where participants received progressive escalations of therapy to reach maximal doses. CI, confidence interval; PCSK9, proprotein convertase subtilisin/kexin type 9

In the subsequent meta-analysis of real-world evidence data, observational studies with unavailable proportions of treated patients by sex, although implying sex differences in the treatment of FH, were excluded. Characteristics of patients from the remaining 25 observational studies are reported in *Table 1*.6–8,10,11,20–40 The majority of studies were published after the year 2016 (introduction of ICD-10 codes for FH) (n = 21). Excluding one large multi-national cohort,6 a total of 13 countries were represented in the sex differences in the treatment of FH meta-analyses, including Norway (n = 3), France (n = 3), Spain (n = 3), USA (n = 3), Canada (n = 2), and UK (n = 2), among others. A substantial number of studies comprised reports from national registries (n = 10), where ascertainment of FH was predominantly through a combination of clinical and genetic criteria (*Table 1*). Quality of included studies, as assessed by the EPHPP tool, was predominantly moderate or strong. Sex differences in treatment with LLT in observational studies are shown in *Figure 3*. Meta-analysis of data from the 25 studies (129 441 participants; 53.4% females) found that females with FH were less likely to be on LLT compared with males [OR .74 (95% CI .66–.85)], despite substantial heterogeneity ($I2$ = 90%). Age and previous history of ASCVD were not significantly different between males and females (data

not shown). Mean LDL-C reductions in mmol/L and in percent change were compared between males and females as depicted in *Figure 4*. On average, LDL-C reductions inferred from baseline lipid values after treatment were greater in males than in females [mean difference in absolute LDL-C reduction of .18 mmol/L (.32–.05) mmol/L, and mean difference in percent LDL-C reduction of 3.42% (5.19–1.66)% greater in males vs. females] (*Figure 4*). This did not translate, however, in a statistical significant difference in absolute LDL-C reductions between sexes [−3.37 mmol/L (−3.17, −3.58) in males vs. −3.21 mmol/L (−2.95, −3.47) in females; *P* = .33] (*Figure 5*).

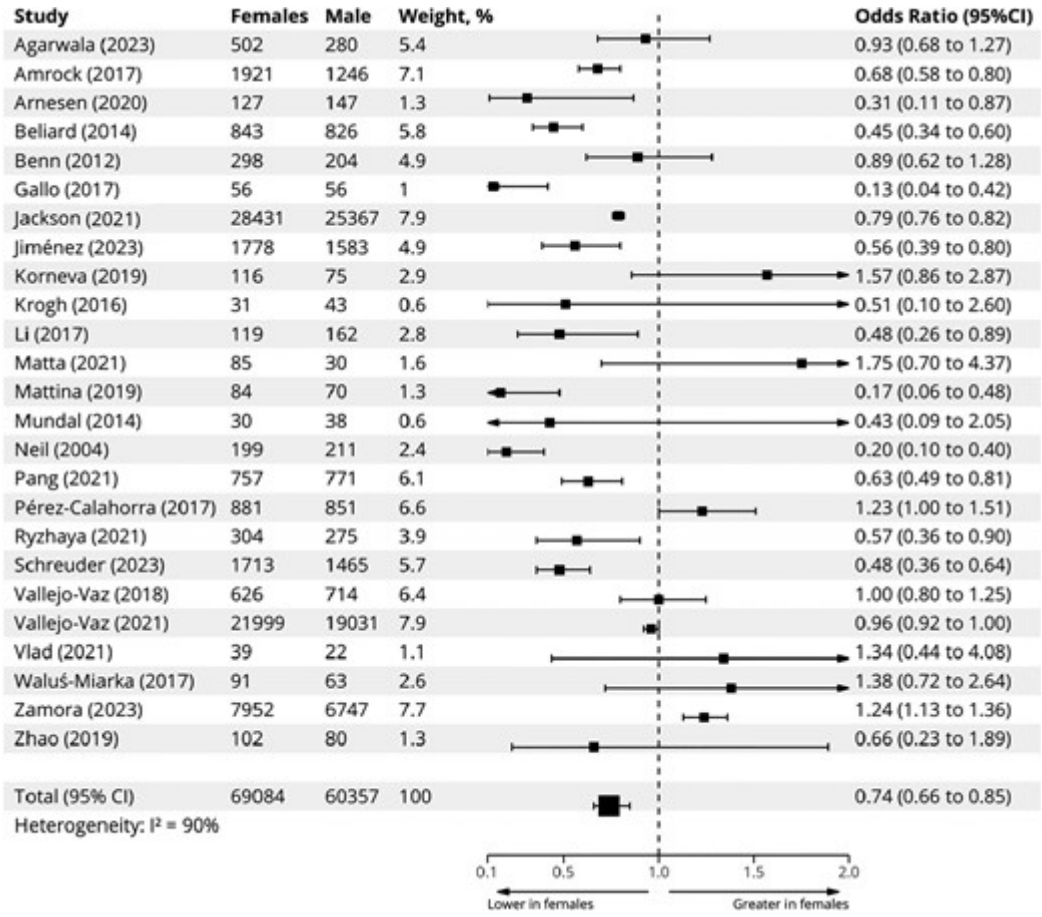


Figure 3

Meta-analysis of sex differences in treatment with lipid-lowering therapies in observational studies. Squares represent study-level odds ratios; horizontal lines represent 95% confidence intervals; large square represents pooled odds ratio derived under the random-effects model. CI, confidence interval

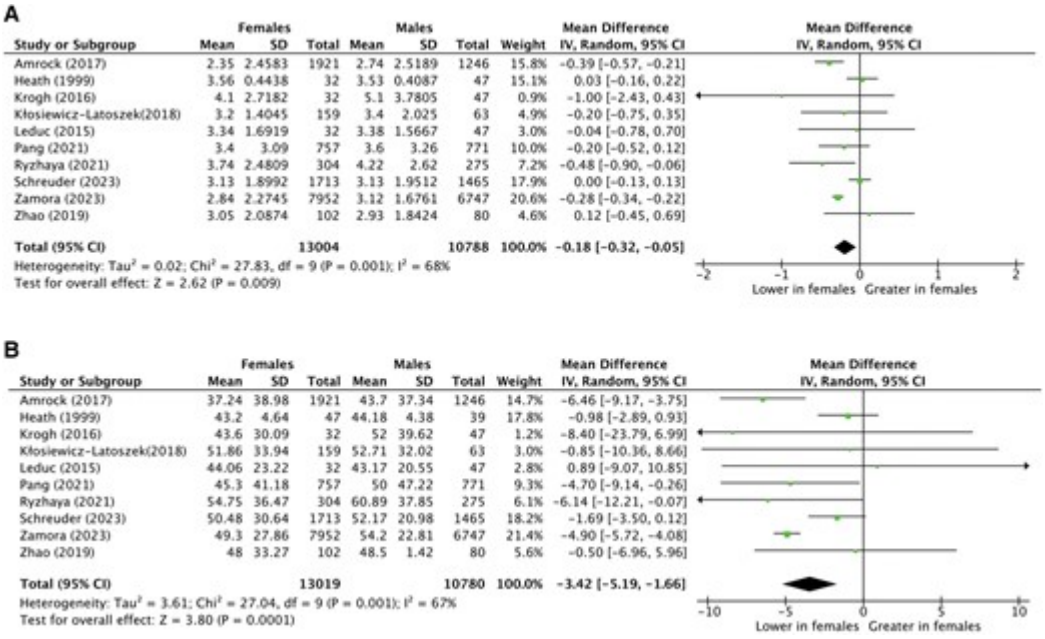


Figure 4

Sex differences in LDL cholesterol reductions in males and females in observational studies included in the systematic review of sex differences in the treatment of familial hypercholesterolaemia with lipid-lowering therapies. Panel (*A*) depicts sex differences in mean LDL cholesterol reduction (mmol/L) reported in observational studies. Panel (*B*) depicts sex differences in mean LDL cholesterol reduction (%) from baseline levels reported in observational studies. CI, confidence interval; SD, standard deviation

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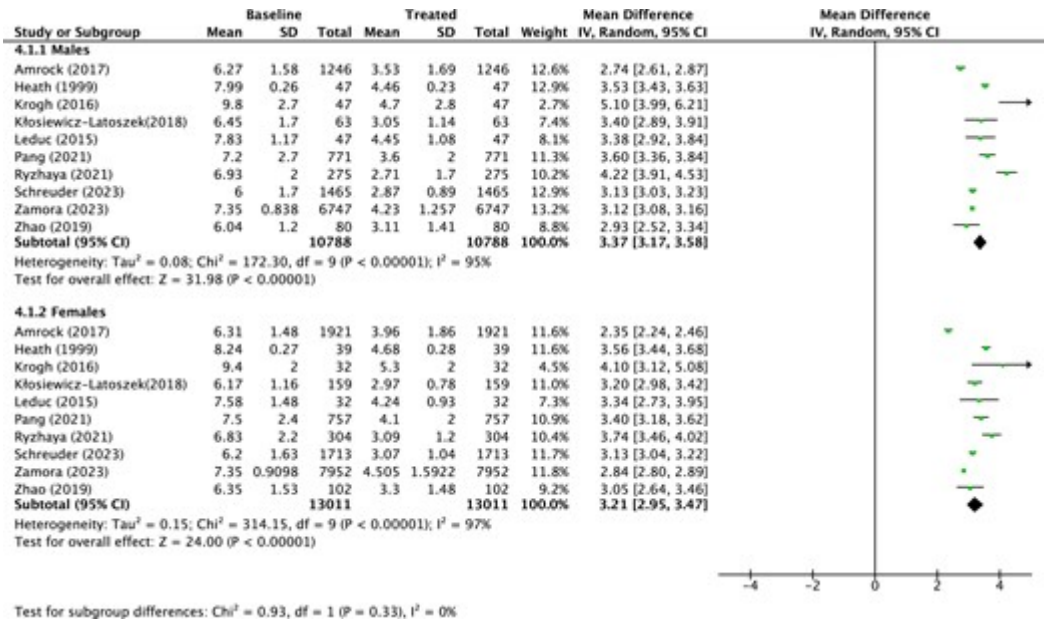

Figure 5

Absolute LDL cholesterol reductions (mmol/L) in males and females in observational studies included in the systematic review of sex differences in the treatment of familial hypercholesterolaemia. This figure depicts difference in means of LDL cholesterol from baseline to follow-up measurements reported in observational data. Squares represent mean differences; horizontal lines show 95% confidence intervals. Area of the square is proportional to the inverse variance of the estimate. Diamonds represent pooled estimates with 95% confidence intervals derived under the random-effects model. Solid vertical line indicates null effect. Test of subgroup differences refers to variations in the difference of means between male and female subgroups; *P*-values <.1 are considered significant. CI, confidence interval; SD, standard deviation

Country-specific estimates of sex differences in the treatment of FH with LLT showed heterogeneity in data, whereby in a majority of the 13 countries represented, with the exception of Argentina, Poland, Romania, and Russia, females were less likely to be treated than males (see Supplementary data online, *Table S2* and *Figure S3*). However, in subgroup analyses of sex differences in treatment with LLT by WHO geographical location demonstrated that in all regions (Americas, Europe, Western Pacific, and International), females with FH were less likely to be on LLT compared with males with FH (see Supplementary data online, *Figure S4*). They were also less likely to be treated compared with males in studies where a majority of participants (>50%) were diagnosed using genetic testing vs. phenotypical/clinical diagnosis (see Supplementary data online, *Figure S5*). A subgroup analysis of sex differences in treatment was further performed by year of publication of studies included, using year 2016 as a cut-point. There were no significant sex disparities between pooled results obtained before and after 2016 (P = .06, Supplementary data online, *Figure S6*). Similar findings were obtained when stratifying by study sample size, with

fewer vs. more than 1000 patients used as a cut-point (P = .23, Supplementary data online, *Figure S7*).

The impact of various types and doses of LLTs between sexes was investigated next (summary estimates in Supplementary data online, *Table S3*). Using random-effects estimates, comparable trends were observed for all medication classes and intensity, with females with FH less likely to be treated with statins [OR .79 (.69–.92)], particularly high-intensity statins [OR .66 (.57–.76)], ezetimibe [OR .67 (.57–.78)], statins and ezetimibe [OR .64 (.48–.86)], PCSK9 inhibitors [OR .70 (.54–.91)], and two or more LLTs [OR .67 (.53–.84)] (see Supplementary data online, *Table S4* and *Figures S8–S11*). This observed trend seemed to diminish, however, with year of publication (see Supplementary data online, *Figure S12*).

In achievement of guideline-recommended lipid targets or thresholds, females were also less likely to reach ≥50% reduction in LDL-C from baseline [OR .78 (.54–1.13)], an LDL-C < 2.5 mmol/L [OR .85 (.74–.97)], or an LDL-C < 1.8 mmol/L [OR .64, (.43–.97)] (*Figure 6* and Supplementary data online, *Table S4*).

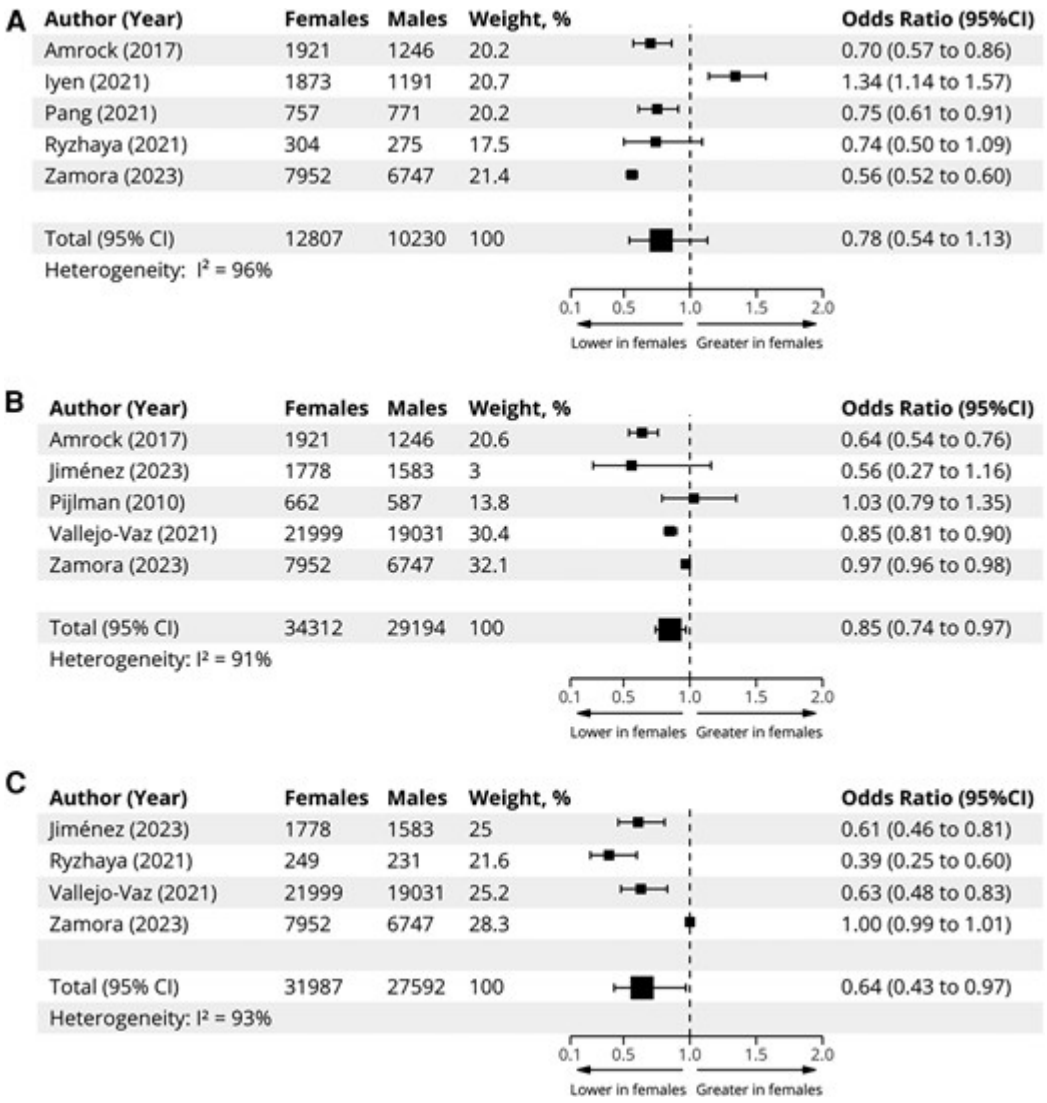

Figure 6

Meta-analyses of sex differences in LDL cholesterol reduction target attainment. Panel (*A*) depicts sex differences in attainment of ≥50% reductions in LDL cholesterol. Panel (*B*) depicts sex differences in attainment of an LDL <2.5 mmol/L. Panel (*C*) depicts sex differences in attainment of an LDL <1.8 mmol/L. Small squares indicate study-level estimates of sex differences in treatment (odds ratios); large squares represent pooled odds ratio derived under random-effects models; horizontal lines represent 95% confidence intervals; vertical dashed line represents null effect. CI, confidence interval

From all 133 studies included in this systematic review of sex differences in the treatment of FH, 57 studies reported data on CVD outcomes and were included in a meta-analysis of MACE. Characteristics of patients from these studies (117 953 participants) are shown in *Table 2*.6,10,20,30,35,38,40–90 Studies followed participants from a range of 12 weeks to 15 years. Pooling these studies (*Figure 7*) with 20 575 events, males with FH were identified as having an upward of two-fold greater relative risk of MACE compared with females (OR 2.16 [1.89–2.47]) and a significantly stronger risk of myocardial infarction (MI) [OR 2.81 (2.54–3.12)], with little heterogeneity between studies ($I2$ = 0%, P = .76). Males also had greater relative risk of coronary heart disease [OR 2.22 (1.85–2.66)], ASCVD [OR 1.94 (1.71–2.19)], and cardiovascular mortality [OR 2.45 (1.47–4.08)]. There were no differences in risk of stroke or peripheral vascular disease between males and females, in 10 studies (72 479 participants; 1809 events) for stroke and nine studies (62 487 participants; 1569 events) for peripheral vascular disease.

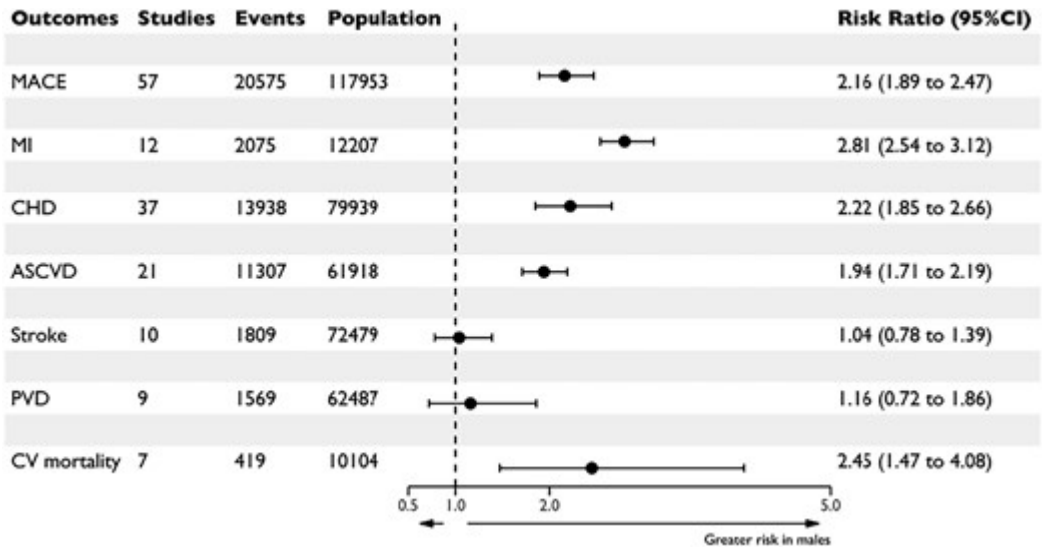

Figure 7

Risk of major adverse cardiovascular events in males vs. females with familial hypercholesterolaemia. This figure depicts pooled estimates (circles) with 95% confidence intervals (horizontal lines) for comparisons of the risk of major adverse cardiovascular events in males vs. females with familial hypercholesterolaemia. All pooled estimates are derived using inverse-

variance weighting incorporating random-effects. ASCVD, atherosclerotic cardiovascular diseases; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular events; MI, myocardial infarction; PVD, peripheral vascular disease.

Table 2

Characteristics of the 57 studies included in the meta-analysis of sex differences in major adverse cardiovascular events in risk of familial hypercholesterolaemia

First author	Year	Study design	Participants	Diagnosis criteria	Males, *n*	Females, *n*	CVD outcomes	Follow-up time
Agarwala20	2023	Retrospective cohort	HeFH	DLCN SB MEDPED AHA Genetic	280	502	Premature ASCVD	NR
Ahmad41	2016	Retrospective cohort	HeFH	Genetic	42	51	Premature CHD	NR
Allard42	2014	Retrospective cohort	HeFH	DLCN	180	229	CVD	NR
Alonso43	2014	Registry	HeFH	Genetic	921	1039	CVD	NR
Beaumont44	1976	Cross-sectional	FH	Phenotypic	158	116	IVD: Angina, MI, PVD	NR

First author	Year	Study design	Participants	Diagnosis criteria	Males, *n*	Females, *n*	CVD outcomes	Follow-up time
Benn10	2012	Cross-sectional	HeFH	DLCN Genetic	204	298	CAD	NR
Berard45	2019	Retrospective cohort	HeFH	DLCN	35	32	Premature ASCVD	NR
Bertolini46	2013	Retrospective cohort	HeFH HoFH	DLCN Genetic	818	951	CHD	NR
Besseling47	2014	Registry	HeFH	Genetic	6848	7435	CVD	NR
Bhatnagar48	2000	Retrospective cohort	HeFH	SB	183	197	Angina, MI, CABG, Stroke, CHD, CVD	NR
Bogsrud49	2019	Registry	HeFH	Genetic	307	407	MI, CHD	11.1 ± 7.9 years
Bowden50	1994	Retrospective cohort	HeFH	Phenotypic	48	67	CAD	NR
Carmena51	1996	Retrospective cohort	HeFH	Phenotypic	45	53	ASCVD	NR
Chan52	2015	Cross-sectional	HeFH	Phenotypic	171	219	CAD	NR

First author	Year	Study design	Participants	Diagnosis criteria	Males, *n*	Females, *n*	CVD outcomes	Follow-up time
				Genetic				
De Sauvage Nolting53	2003	Cross-sectional	HeFH	DLCN Genetic	287	229	CVD	NR
Doi54	2021	Retrospective cohort	HeFH	Genetic JAS	116	116	MI, revascularization	NR
Duell55	2019	Registry	HeFH	DLCN Genetic MEDPED SB	744	1156	ASCVD	20 ± 11 months
Ershova56	2017	Retrospective cohort	HeFH	DLCN	7	23	CAD, MI	NR
Firth57	2008	Retrospective cohort	HeFH	Phenotypic Genetic	488	581	Angina, MI, IHD, Stroke, TIA, PVD, Death	NR
Hill58	1990	Cross-sectional	HeFH	Phenotypic	CAD data:	CAD data:	Angina, CAD, MI,	NR

First author	Year	Study design	Participants	Diagnosis criteria	Males, *n*	Females, *n*	CVD outcomes	Follow-up time
					115	173	Stroke	
Hirobe59	1982	Cross-sectional	HeFH	Phenotypic	30	22	CAD	NR
Holmes60	2005	Retrospective cohort	HeFH	SB	173	215	CVD	NR
Hoogerbrugge61	1999	Clinical trial	HeFH	Phenotypic	20	20	CAD	12 weeks
Hopkins62	2001	Registry	HeFH	MEDPED	112	150	Premature CAD	NR
Iyen63	2019	Retrospective cohorty—registry	FH	DLCN SB	6578	7519	CVD	13.8 (8.4–17.7) years
Jansen64	2004	Retrospective cohorty—registry	HeFH	DLCN MEDPED SB Genetic	1179	1221	CVD	CVD+: 4.7 (2.4–9.0) years CVD−: 3.2 (1.2–6.5)

First author	Year	Study design	Participants	Diagnosis criteria	Males, *n*	Females, *n*	CVD outcomes	Follow-up time
								years
Khoury65	2021	Bi-directional cohort	FH	SB Genetic	891	888	CVE	NR
Li30	2017	Retrospective cohort	FH	DLCN Genetic	162	119	CAD, Premature CAD	NR
Mabuchi66	1977	Cohort	HeFH	Phenotypic	IHD data: 37	IHD data: 46	IHD	NR
Michikura67	2017	Cross-sectional	HeFH	Phenotypic	53	77	CAD	NR
Miettinen68	1988	Retrospective cohort	HeFH	Phenotypic	48	48	CAD, CAD Mortality	15 years
Minam e69	2019	Prospective study	HeFH	Genetic	75	131	MACE	Median (IQR) 3.7 (2.7–6.8) years
Mohrschladt 70	2004	Retrospective cohort	FH	Phenotypic	190	210	CVD	8 years

First author	Year	Study design	Participants	Diagnosis criteria	Males, *n*	Females, *n*	CVD outcomes	Follow-up time
Mundal[71]	2016	Registry	HeFH HoFH	Genetic	2693	2845	CVD hospitalizations	Median (IQR) 5 (1–9) years
Neil[72]	2008	Cross-sectional study—registry	HeFH	SB	1650	1732	Angina, CHD, CVD mortality, MI	Median M: 14.5 years F: 14.1 years
Nenseter[73]	2011	Retrospective cohort	HeFH	Genetic	68	44	CHD	NR
Panagiotakos[74]	2003	Prospective cohort	HeFH	MEDPED	295	344	CHD	15 years
Pang[75]	2018	Retrospective cohort—registry	HeFH	Genetic	399	476	CAD	NR
Perak[76]	2016	Retrospective cohort	HeFH	AHA	1559	2291	ASCVD, CHD	≥10 years
Pérez-Calaho	2017	Cross-sectional	HeFH	DLCN	851	881	CVD	NR

First author	Year	Study design	Participants	Diagnosis criteria	Males, *n*	Females, *n*	CVD outcomes	Follow-up time
rra35		analysis of registry data						
Perez de Isla77	2017	Registry	HeFH	Genetic	1087	1317	ASCVD	5.5 ± 3.2 years
Perez Garcia 78	2018	Retrospective cohort	HeFH HoFH	Genetic	67	66	CHD	NR
Pisciotta79	2005	Prospective cohort	HeFH	Phenotypic	103	146	CAD	NR
Pitsavos80	2004	Retrospective cohort	HeFH	Phenotypic	295	344	CHD	6 ± 3 years
Ramos 81	2020	Retrospective cohort	FH-phenotype	Phenotypic	3047	4385	ASCVD	NR
Sánchez-Ramos 82	2021	Prospective cohort	HeFH	Phenotypic	602	105	MACE	6.6 ± 3.6 years
Seed83	1990	Retrospective cohort	HeFH	SB	61	54	CHD	12 months

First author	Year	Study design	Participants	Diagnosis criteria	Males, *n*	Females, *n*	CVD outcomes	Follow-up time
Silva84	2016	Prospective cohort	FH	Genetic	302	516	CVD	1 year
Simonen85	1987	Retrospective cohort	HeFH	Phenotypic	49	48	Angina, CAD	NR
Slack86	1969	Retrospective cohort	HeFH	Phenotypic	51	53	IHD, IHD mortality	NR
Tada87	2023	Retrospective cohort	HeFH HoFH	JAS Genetic	490	560	MACE	12.6 (9.1–17.4) years
Vallejo-Vaz6	2021	Retrospective cross-sectional—registry	HeFH	DLCN Genetic MEDPED SB Canadian JAS	19 031	21 999	CAD, PAD, Premature CAD, Stroke	NR
Vlad38	2021	Prospective cohort	FH	SB DLCN MEDPED	CHD data in 61	CHD data in 61	ASCVD, CHD, PAD, Stroke	2 years
Vuorio	1997	Registry	HeFH	Phenot	73	106	CHD, MI	NR

First author	Year	Study design	Participants	Diagnosis criteria	Males, *n*	Females, *n*	CVD outcomes	Follow-up time
88				ypic Genetic				
Wierzbicki89	2000	Retrospective cohort	HeFH	SB	66	46	CHD	≥6 years
Yaman 90	2020	Cross-sectional	HeFH	DLCN	119	248	CHD	NR
Zhao40	2019	Bi-directional cohort	FH	Canadian Genetic	80	102	Premature MI	≤1 year

AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; CVE, cardiovascular event; DLCN, Dutch Lipid Clinic Network; F, females; FH, familial hypercholesterolaemia; FU, follow-up; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; IHD, ischemic heart disease; IQR, interquartile range; IVD, ischaemic vascular disease; JAS, Japanese Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol; M, males; MACE, major adverse cardiac events; MEDPED, Making Early Diagnosis to Prevent Early Deaths; MI, myocardial infarction; NR, not reported; PAD, peripheral arterial disease; PVD, peripheral vascular disease; SB, Simon Broome; UK, United Kingdom; USA, United States of America.

From the 133 studies included in the qualitative synthesis, i.e. in studies that were found to have data on sex differences in the treatment of FH, 57

were found to have quantitative data on the risk of MACE outcomes for meta-analysis.

a56 countries (of 66) participating in the European Atherosclerosis Society's Familial Hypercholesterolaemia Studies Collaboration.

Discussion

In the present study, important sex disparities in treatment and lipid target achievement in patients with FH were observed and should be taken into consideration. With data in more than 129 000 patients, this is the largest systematic review performed to date providing evidence for sex differences in treatment with LLT among individuals with FH. These results emphasize the importance of considering sex in risk-stratifying patients with FH and highlight the need for sex-specific strategies for CVD prevention.

In clinical trials using fixed doses of LLTs, males and females with FH displayed similar response to LDL-C lowering medications. Despite this, in observational studies, females were treated less intensively and were less likely to reach guideline-recommended LDL-C targets (see *Structured Graphical Abstract*). This was independent of WHO geographical location and the proportion of females studied, although the observed trend seemed to diminish with year of publication, suggesting that initiatives by national registries as well as international organizations such as the Family Heart FH Foundation and the FHSC led by the European Atherosclerosis Society may be having an impact to lessen these sex disparities.91,92 Further research is nevertheless needed to identify causes underlying these disparities.

The reasons behind these sex differences are not fully understood but are likely multifactorial. In terms of direct care, one possibility could be that females are reluctant to be treated with LLTs or under-estimate their own health risk with FH. However, our group has previously shown that females do not appear to minimize this risk associated with FH or CVD.5 Other reasons include adverse effects. It has been well described that in general, females report a significantly higher number of side events with LLT than

males which may impede up-titration to optimal LLT.36 Healthcare providers might also play a role. In a nationwide multicentre Spanish registry with 3361 adult patients with FH, females had a 49% lower chance of being prescribed a PCSK9 inhibitor than males.27 However, prior studies on FH report no sex differences in adherence to LLT.93,94

In FH, LLT is recommended to reduce the risk of ASCVD without differences according to sex. Evidence from clinical trials of LLT in patients with FH indicates that statins are equally effective in both males and females in the prevention of ASCVD in high-risk populations. In the present meta-analysis, however, we confirm that males and females with FH are less likely to reach guideline-mandated therapeutic thresholds for primary and secondary prevention, with females being treated less intensively than males. These findings support recent studies where females received less high-potency statins and fewer females reached lipid targets of LDL <2.0 mmol/L.7 This lower intensity LLT was especially evident for females in secondary prevention. The differences in goal achievement can be partly explained by the finding that females with FH have higher LDL-C levels from an earlier age,95 are diagnosed 3–7 years later than males, and seldom use maximally tolerated statin doses or combination LLT.6 As a result, achievement of recommended LDL-C treatment goals is subsequently lower. These disparities in FH care impact ASCVD risk, with registry data showing the highest excess risk among younger females with FH.11,96

In the present study, even though females with FH were treated less intensively and reached their LDL-C goals less frequently, males had more than two-fold greater cardiovascular risk. This disparity was consistent across various subgroups and outcomes, including MI, ASCVDs, and cardiovascular death. The association between FH and ASCVD is widely recognized, but there has been uncertainty regarding equality of this excess risk in males and females. While an early report from the Copenhagen General Population Study found no meaningful difference in risk estimates between sexes,10 the UK Simon Broome and Norwegian registries have since documented greater cardiac morbidity and mortality among

females.11,96 More recently, a multi-national cross-sectional study of FH registries demonstrated a greater risk of prevalent CAD in males.6 Part of the uncertainty in the evidence may be attributed to disharmony in outcomes examined by previous individual studies and the referral bias seen in disease-specific registries compared with general population settings. Further, females are generally underrepresented in FH and CVD literature, resulting in a lack of statistical precision in risk estimates. Finally, absence of direct comparisons between males and females with FH has made interpreting the limited available data challenging. In this meta-analysis, we aimed to address these shortfalls in the literature.

The sex differences reported here potentially reflect a culmination of genetic and hormonal factors, sex-specific health behaviours, and some systemic determinants. For example, our findings might suggest that other cardio-protective factors, such as pre-menopausal status, higher HDL cholesterol levels, lower prevalence of other cardiovascular risk factors, such as tobacco, or higher levels of triglycerides and remnant lipoprotein cholesterol in males might play a role. In fact, males in the present study may have had more cardiovascular risk factors than their female counterparts,38 which have been shown to exert cumulative97 and sex-specific impacts on CVD risk among those with FH. While some risk estimates included in our analyses accounted for these factors, it is likely that some were not fully adjusted for. Excess risk observed in males may have also been due to differences in treatment with LLT, as we were not able to account for treatment intensity, efficacy, or duration in our analyses. This explanation may be less likely, however, given our current results suggesting that males with FH are treated earlier98 and more aggressively than female counterparts and are more likely to reach cholesterol reduction targets.27 Finally, it may be possible that a greater proportion of females included in studies represented non-index cases given the earlier onset of cardiovascular events in males. Studies have demonstrated that affected relatives are detected several years earlier, with fewer cardiovascular risk factors and improved cardiovascular outcomes.6

Interestingly, no difference between males and females was found in the risk of stroke and peripheral vascular disease, contrasting patterns seen in the general population.99–101 A potential explanation for this may be similar rates of predisposing factors such as atrial fibrillation and heart failure among males and females with FH.102 Alternatively, it is possible that factors such as age, socioeconomic status, and lifestyle behaviours interact with sex and gender to impact the likelihood of stroke and peripheral vascular disease.103 If that were the case, uncovering these potentially protective determinants would present an important priority for future research.

This study has some strengths and limitations that merit consideration. Among its strengths are its exhaustive search, large sample size, diversity of study populations, extensive sensitivity investigations, and the important information it brings to the field. In terms of limitations, first omission of relevant reports cannot be ruled out despite extensive search efforts. However, the large number of studies included in our primary analysis made these results robust to the inclusion of any single investigation. Second, studies reporting significant associations between sex and cardiovascular outcomes might be more likely to be published. Third, it is recognized that the trim-and-fill method may not be valid in the presence of excess heterogeneity between studies.19 A high degree of heterogeneity ($I2 > 70\%$) was observed for several analyses, likely explained by difference in studies design, diagnostic criteria, and endpoint definitions, suggesting bias between studies (see Supplementary data online, *Figure S13*). This is consistent with the meta-analysis being a study-level rather than a patient-level meta-analysis, with both retrospective and prospective studies included. We anticipated and accounted for this heterogeneity using random-effects models. Finally, while our study evaluated sex differences in outcomes in patients with FH, we were unable to account for gender identity and other important aspects of intersectionality in our analyses. Accordingly, these present pressing areas for future research.

Conclusions

The present study found than males and females with FH show similar response to LDL-C lowering medications. Despite this, females seemed less likely to be treated intensively and to reach guideline-recommended LDL-C targets. A better understanding of drivers of sex-related disparities in FH treatment is needed. Identifying these imbalances will allow us to reduce barriers to care and improve survival in individuals with FH.

9. Sex-Specific Functional Status Decline and Outcomes in Mild-to-Moderate Aortic Stenosis: Results From the PROGRESSA Study

Introduction

Calcific aortic valve stenosis (AS) is a leading cause of morbidity and mortality in high-income countries.**1** Due to the growing number of older people, the health care and socioeconomic burden related to AS is expected to increase dramatically in the next 2 decades.**1** There are no proven pharmacotherapies to prevent the development or the progression of AS, thus, surgical or transcatheter aortic valve replacement (AVR) remains the only effective therapeutic treatment for patients with severe AS.**2**,**3**

In patients with severe AS, AVR is recommended (Class I) in presence of symptoms and/or left ventricular (LV) systolic dysfunction (LV ejection fraction [LVEF] <50%).**2**,**3** In asymptomatic patients with severe AS, AVR may be considered (class IIa or IIb) in presence of very severe AS, fast progression rate of valve stenosis, markedly elevated brain natriuretic peptide (BNP), or decline in LVEF below 60%.**2**,**3** However, in current guidelines, the progression or decline in functional/health-related parameters are not considered as triggers for AVR in asymptomatic patients with AS.**2**,**3** Moreover, previous studies have reported sex-based differences in the clinical presentation and outcomes of severe AS, including more heart failure symptoms, late referral for AVR, and worse outcomes following

surgical AVR in female patients.**4-7** However, it remains unclear whether the decline in functional status during the course of AS differs between women and men.

In this prospective observational study including patients with mild-to-moderate AS at baseline, we investigated: 1) the association of hemodynamic AS progression rate with changes in functional status according to sex; and 2) the association of functional status decline with the composite of death or AVR according to sex.

Methods

Study population

The purpose and design of the PROGRESSA (Metabolic Determinants of the Progression of Aortic Stenosis, **NCT01679431**) study were previously described.**8**,**9** Briefly, patients with age ≥18 years and at least mild AS (ie, peak aortic jet velocity [Vpeak] ≥2.0 m/s) were prospectively recruited and undergo a comprehensive Doppler echocardiography annually. For the present analysis, patients were excluded if they had: 1) severe and/or symptomatic AS, and/or indication for AVR; 2) moderate or greater aortic regurgitation, or significant mitral valve disease (stenosis or regurgitation); 3) LVEF <50%; and 4) if they are pregnant or lactating. The study was approved by the Ethics Committee of the Institut universitaire de cardiologie et de pneumologie de Québec, and all patients signed a written informed consent at the time of enrollment. Among the 345 patients recruited until October 31, 2018, 244 patients with mild-to-moderate AS had completed at least one follow-up with comprehensive clinical and imaging evaluation, and thus were included in the present subanalysis of the PROGRESSA study.

Clinical and laboratory data

Clinical data included age, sex, height, weight, body surface area (BSA), body mass index, systolic and diastolic blood pressures, documented diagnoses of comorbidities (**Supplemental Methods**). Plasma levels of

glucose, creatinine, N-terminal pro b-type natriuretic peptide (Nt-proBNP), standard lipid profile, apolipoprotein B, apolipoprotein A-I, and lipoprotein(a) [Lp(a)] were measured (**Supplemental Methods**). Furthermore, we calculated the ratio of Nt-proBNP between the measured serum level and the maximal normal level of Nt-proBNP for age and sex, as previously described.**10** A NT-proBNP ratio >1 indicates an abnormal/elevated serum level of Nt-proBNP.**10**

Functional status data

Functional status was assessed at baseline and then annually using the NYHA functional class **11** and the Duke Activity Status Index (DASI).**12** The DASI is a self-administered questionnaire developed for assessment of functional status, which includes a 12-item questionnaire related to physical function and daily activities of living (ie self-care, ambulation, household tasks, sexual function, and recreational activities).**12**,**13** The sum of the points provided by each weighted item composes the DASI score, ranging from 0 to 58.2. Higher scores indicate better functional capacity. Metabolic equivalent was estimated as previously described.**12** Functional status data were prospectively collected by experienced nurses and trained clinical research personnel.

Echocardiographic data

Comprehensive Doppler echocardiography exams were performed using commercially available ultrasound systems and images were analyzed in a core laboratory by experienced readers (**Supplemental Methods**). The aortic valve phenotype (ie, bicuspid versus tricuspid) was recorded. Stroke volume was calculated by multiplying the LV outflow tract area by the flow velocity-time integral and was indexed to BSA (SVi). The Doppler-echocardiographic indices of AS severity included Vpeak, mean pressure gradient, aortic valve area (AVA) calculated by the standard continuity equation and indexed AVA to BSA as recommended by guidelines.**14** The grading of AS severity and

other echocardiographic measures were detailed in the **Supplemental Methods**.

Study endpoints

The study primary endpoint was defined as the composite of death from any cause or AVR throughout the study period (from baseline to the last follow-up). The decision of AVR was left to the discretion of the treating physician. The outcome data were collected prospectively through review of medical records and patient interviews. All patients included in the present study had at least one follow-up visit (≥1 year) and no patients were lost at follow-up prior to the occurrence of clinical outcome or study completion.

Statistical analysis

Continuous variables were presented as mean ± SD or median (IQR) for non-normally distributed variables. Continuous variables were compared between groups with Student's *t*-test or with Wilcoxon-Mann-Whitney test. Categorical variables were presented as frequencies and percentages and were compared with chi-square test or Fisher's exact test. Changes in functional-related instruments over time were compared with baseline visit within each AS progression group using paired Student's *t*-test or Wilcoxon matched-pairs signed-rank test, as appropriate. Mixed model for repeated measures was used to compare the changes in DASI score at each follow-up time point.

Linear mixed models were used to determine the association of sex and hemodynamic progression rate of AS with the change of continuous dependent variables over time, specifically the change in DASI score. Linear generalized mixed models were used to determine the association of sex and hemodynamic progression rate of AS with the change of categorical dependent variables over time, specifically the change in NYHA functional class. The fixed effect included sex, hemodynamic parameters of AS severity (ie, Vpeak measured at each visit), and the number of annual visits. The random effects included patients' study identification numbers and a

random intercept to account for inherent variability among individual. The models were adjusted for age, body mass index, hypertension, diabetes, metabolic syndrome, coronary artery disease, history of atrial fibrillation, stroke volume index, and E/e' ratio as fixed factors. Results were presented as OR or coefficients, standard error, and 95% CIs.

Time-to-event analyses were performed between the baseline and last follow-up study visits. To account for missing data during the study period (11% of missing DASI score), multiple imputations by predictive mean matching using chained equations were conducted.**15** Time-to-events data were analyzed by averaging the parameter estimates across the imputed data sets and pooling individual results using Rubin's combination rules.**16** The estimates of cumulative incidence of death or AVR according to functional status decline were calculated using the Kaplan-Meier method and compared using the log-rank test. Univariable and multivariable Cox proportional hazards models were performed to determine the association between functional status decline with the composite of death or AVR. All survival analyses were performed both on the imputed and nonimputed data sets to ensure the robustness of our findings. Results were presented as HR with 95% CIs. Multivariable Cox proportional hazards models were adjusted for age, sex, hypertension, diabetes, plasma level of Lp(a), bicuspid aortic valve, LV mass index, E/e' ratio, and included NYHA class, DASI score, and peak aortic jet velocity as time-dependent measures. The variables selected for multivariable analyses were clinically relevant variables or variables associated with risk of events in univariable analyses (ie, $P < 0.10$). A 2-tailed P value < 0.05 was considered significant. Statistical analyses were performed with Stata software, version 18.0 (StataCorp).

Results

Study population

Among the 244 patients (mean age 64 ± 14 years, 29% female) included in the present study, most had no or mild symptoms (98% NYHA functional

class I or II) at baseline. Four (2%) patients with mild AS had more than mild symptoms (NYHA functional class III), with concurrent comorbidities, including obesity, which may have contributed to their symptoms. DASI was available for 219 (89%) patients, with a mean score of 41.2 ± 14.1 points, suggesting moderately good functional status at baseline.

Table 1 describes the baseline characteristics of the study population according to sex. Compared to men, women were younger and had a lower prevalence of hypertension, history of smoking, coronary artery disease, and atrial fibrillation, along with significantly lower plasma levels of Nt-proBNP ratio and high-sensitivity troponin T (all, $P \leq 0.01$) (**Table 1**). Despite the lower prevalence of comorbidities, women had worse functional status at baseline, characterized by a higher NYHA class ($P = 0.01$) and lower DASI score compared to men ($P = 0.006$) (**Table 1**). The degree of AS severity was comparable between women and men (VPeak: 2.6 ± 0.4 m/s vs 2.7 ± 0.5 m/s; $P = 0.08$) (**Table 1**). As expected, LV mass index was significantly lower in women than in men ($P < 0.001$), but women had more LV hypertrophy (51% vs 33%; $P = 0.008$) (**Table 1**).

Table 1 Baseline Characteristics of the Study Population	**All Patients (N = 244)**	**Women (n = 71, 29%)**	**Men (n = 173, 71%)**	***P* Value**
Clinical data				
Age, y	64 ± 14	61 ± 16	66 ± 12	**0.03**
Body surface area, m2	1.90 ± 0.21	1.69 ± 0.13	1.98 ± 0.18	**<0.001**
Body mass index, kg/m2	29 ± 5	28 ± 5	29 ± 4	**0.009**
NYHA functional class				**0.009**
I	133 (55)	28 (39)	105 (61)	
II	107 (44)	41 (57)	66 (38)	
III	4 (2)	2 (3)	2 (1)	
Duke Activity Status	41.2 ± 14.1	37.4 ±	42.8 ±	**0.01**

Table 1 Baseline Characteristics of the Study Population	**All Patients (N = 244)**	**Women (n = 71, 29%)**	**Men (n = 173, 71%)**	***P* Value**
Index score		14.5	13.7	
Metabolic equivalents	7.8 ± 1.7	7.3 ± 1.8	8.0 ± 1.7	**0.01**
Systolic blood pressure, mm Hg	138 ± 19	133 ± 20	139 ± 18	**0.01**
Diastolic blood pressure, mm Hg	77 ± 9	76 ± 9	77 ± 9	0.59
Hypertension	191 (78)	48 (68)	143 (83)	**0.01**
Diabetes mellitus	59 (24)	13 (18)	46 (27)	0.17
Metabolic syndrome	53 (22)	16 (23)	37 (22)	0.88
History of smoking	154 (63)	27 (38)	127 (73)	**<0.001**
Coronary artery disease	74 (30)	11 (15)	63 (36)	**0.001**
History of atrial fibrillation	32 (13)	4 (6)	28 (16)	**0.03**
Medication data				
ACE inhibitors	71 (29)	12 (17)	59 (34)	**0.007**
ARBs	74 (30)	26 (37)	48 (28)	0.17
Beta-blockers	73 (30)	14 (20)	59 (34)	**0.03**
Lipid-lowering agents	159 (65)	38 (54)	121 (70)	**0.01**
Anticoagulants	15 (6)	1 (1)	14 (8)	**0.04**
Laboratory data				
LDL-C, mmol/L	2.20 (1.76-2.75)	2.42 (1.83-3.15)	2.14 (1.75-2.59)	**0.001**
apoB, g/L	0.80 (0.69-0.99)	0.84 (0.72-1.07)	0.79 (0.69-0.96)	**0.02**
apoA-I, g/L	1.49 (1.32-1.67)	1.62 (1.43-	1.44 (1.28-	**<0.001**

Table 1 Baseline Characteristics of the Study Population	**All Patients (N = 244)**	**Women (n = 71, 29%)**	**Men (n = 173, 71%)**	***P* Value**
		1.77)	1.59)	
HDL-C, mmol/L	1.38 (1.19-1.61)	1.54 (1.36-1.72)	1.32 (1.15-1.54)	**<0.001**
Lp(a), mg/dL (n = 177)	14 (6-45)	15 (5-56)	14 (5-45)	0.71
Triglycerides, mmol/L	1.27 (0.89-1.77)	1.23 (0.88-1.75)	1.27 (0.89-1.78)	0.72
Fasting glucose, mmol/L	5.3 (5.0-6.1)	5.1 (4.8-5.7)	5.4 (5.0-6.2)	**0.002**
Creatinine clearance, mL/min	84 (70-97)	88 (71-102)	83 (70-94)	0.14
NT-proBNP, pg/mL	80 (39-196)	90 (43-178)	76 (37-207)	0.45
NT-proBNP ratio	0.7 (0.4-1.6)	0.5 (0.3-0.9)	0.9 (0.4-2.1)	**<0.001**
High-sensitivity troponin T, ng/L	8.1 (5.4-12.7)	5.8 (3.0-7.9)	9.1 (6.0-13.7)	**<0.001**
Echocardiographic data				
Bicuspid aortic valve	58 (24)	23 (32)	35 (20)	**0.04**
Stroke volume index, mL/m2	42 ± 6	42 ± 6	42 ± 6	0.92
Peak aortic jet velocity, m/s	2.6 ± 0.4	2.6 ± 0.4	2.7 ± 0.5	0.08
Mean gradient, mm Hg	16 ± 5	15 ± 5	16 ± 5	0.10
Aortic valve area, cm2	1.31 ± 0.24	1.20 ± 0.22	1.36 ± 0.23	**<0.001**

Table 1 Baseline Characteristics of the Study Population	**All Patients (N = 244)**	**Women (n = 71, 29%)**	**Men (n = 173, 71%)**	***P* Value**
Indexed aortic valve area, cm2/m2	0.69 ± 0.12	0.71 ± 0.14	0.69 ± 0.12	0.25
Mild AS	198 (81)	60 (76)	138 (67)	0.39
LV mass index, g/m2	104 ± 21	95 ± 19	108 ± 21	**<0.001**
LV hypertrophy	91 (39)	36 (51)	55 (33)	**0.008**
E/e' ratio	11.1 ± 3.8	11.3 ± 3.7	11.0 ± 3.8	0.60
LV ejection fraction, %	65 ± 5	66 ± 5	64 ± 6	**0.003**

Values are mean ± SD, n (%), or median (25th–75th percentiles). **Bold** values indicates a significant *P*-value ($P < 0.05$).

ACE = angiotensin-converting enzyme; apoB = apolipoprotein B; apoA-I = apolipoprotein A-I; ARBs = angiotensin receptor blockers; AS = aortic valve stenosis; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); LV = left ventricular; NT-proBNP = N-terminal pro B-type natriuretic peptide.

AS progression, decline of functional status, and effect of sex

During a mean follow-up time of 4.3 ± 2.4 years, the proportion of patients with mild symptoms (NYHA functional class II) remained consistent from 43.9% to 42.2%. Conversely, the proportion of moderate (NYHA functional class III) and severe (NYHA functional class IV) symptoms increased from 1.6%, and 0% to 4.1%, and 1%, respectively. The deterioration in functional capacity was also apparent with a decrease in mean DASI score from 41.2 ± 14.1 to 34.6 ± 13.1 points. The AS progression rate, that is the annualized change in Vpeak, in the whole cohort was: 0.11 m/s/year (range: 0.03-0.21). Thirty-six (15%) patients had fast (Vpeak ≥0.30 m/s/year), 88 (36%) intermediate (Vpeak 0.11-0.29 m/s/year), and 120 (49%) slow (Vpeak <0.11 m/s/year) progression rate. There was no significant difference between men and women in AS progression rate based on Vpeak ($P = 0.06$). However,

the disease progression rate based on mean gradient was significantly faster in men compared to women (P = 0.02) (**Supplemental Figure 1A and 1B**). In addition, the annualized changes in indexed AVA and SVi were comparable between women and men (both, $P \geq 0.18$) (**Supplemental Figure 1C and 1D**). There was also evidence of more severe AS in women and men at last follow-up, with more incidence of low-gradient severe AS in women versus men (35% vs 27%) and more high-gradient severe AS in men versus women (13% vs 7%) (**Supplemental Figure 2**).

Figure 1 shows the change in NYHA functional class between baseline and 5 years of follow-up according to sex. The proportion of symptomatic patients (NYHA functional class ≥II) remained higher in women at 5 years, although there were no statistically significant differences (**Figure 1**). For the same degree of AS hemodynamic progression rate, women had more symptoms than men from baseline to 5 years (**Figure 1**).

NYHA Functional Class According to Sex and AS Progression Rate

Comparison of NYHA functional class at baseline, 2-year, and 5-year follow-up between women and men, and according to hemodynamic progression rate of AS. Intermediate-to-fast versus slow progression rate of AS was defined as annualized change in Vpeak ≥11 or <0.11 m/s/year. ♀ = Women; ♂ = Men. AS = aortic valve stenosis; Vpeak = peak aortic jet velocity.

There was a significant decline in DASI score in both women and men (P < 0.05), with no significant difference in the rate of decline between two groups (P = 0.90) (**Figure 2A**). Although the slope of decline in DASI was comparable between women and men, DASI score remained significantly lower in women vs men from baseline to 5 years (**Figure 2A**). When analyzed according to AS progression rate, women with intermediate-to-fast hemodynamic progression rate (Vpeak increase ≥0.11 m/s/year) had a significantly faster decline in DASI score compared to other groups (**Figure 2B**).

Change in DASI Score According to Sex and AS Progression Rate

Linear prediction of the change in DASI score from baseline to 5-year follow-up between women and men (A), and according to sex and AS progression rate (B). ∗ Indicates significant between-group difference (ie $P < 0.05$). *P* values were obtained after linear mixed analyses. ΔIndicates the change from baseline visit. DASI = Duke Activity Status Index; other abbreviation as in **Figure 1**.

In multivariable analysis, female sex remained significantly associated with the increase in NYHA functional class during follow-up (OR: 14.8; $P < 0.001$) (**Table 2**). The increase in hemodynamic severity of AS (ie Vpeak) during follow-up remained significantly associated with the increase in NYHA functional class (OR: 4.19; $P < 0.001$) (**Table 2**). Female sex and AS hemodynamic severity remained significantly associated with the decline in DASI score during follow-up ($P < 0.001$) (**Table 3**). Of note, bicuspid aortic valve ($P = 0.20$) and LV mass index ($P = 0.08$) were not significantly associated with the increase in NYHA functional class, or the decline in DASI score (all, $P \geq 0.67$). The analysis including Lp(a) measurement is detailed in the **Supplemental Results**.

Table 2Association Between Sex, Change in Hemodynamic Severity of AS, and Worsening of NYHA Functional Class	**Change in NYHA Functional Class (n = 244)**					
	Unadjusted Model			**Adjusted Modela**		
	OR	**SE**	**95% CI**	**OR**	**SE**	**95% CI**
Female	4.96	2.08	2.18-11.3b	14.8	6.08	6.64-33.1b
Peak aortic jet velocity, (per 1 m/s increase)	1.86	0.47	1.13-3.05c	4.19	1.19	2.41-7.31b

DASI = Duke Activity Status Index; other abbreviation as in **Table 1**.

a Adjusted model including age, body mass index, hypertension, diabetes, metabolic syndrome, coronary artery disease, history of atrial fibrillation, stroke volume index, E/e' ratio, and follow-up time. OR is the odds ratio which indicates the risk of increase in NYHA functional class for each per-unit change in variables (ie female sex, NYHA class, and peak aortic jet velocity). SE is the standard error.

b $P < 0.001$.

c $P \leq 0.01$.

Table 3Association Between Sex, Change in Hemodynamic Severity of AS, and Decline in DASI Score	**Change in DASI Score (n = 237)**					
	Unadjusted Model			**Adjusted Modela**		
	Coefficient	**SE**	**95% CI**	**Coefficient**	**SE**	**95% CI**
Female	−5.54	1.87	−9.19 to −1.88 c	−10.3	1.37	−12.9 to −7.56 b
Peak aortic jet velocity, (per 1 m/s increase)	−6.21	0.82	−7.81 to −4.61 b	−3.51	0.83	−5.13 to −1.89 b

Abbreviation as in **Tables 1** and **2**.

a Adjusted model including age, body mass index, hypertension, diabetes, metabolic syndrome, coronary artery disease, history of atrial fibrillation, stroke volume index, E/e' ratio, and follow-up time. Coeff. is the fixed effect, which indicates the change in DASI score for each per-unit change in

variables (ie, female sex and peak aortic jet velocity). SE is the standard error of the estimate regression coefficient.
b $P < 0.001$.
c $P < 0.01$.

Risk of clinical events according to functional status decline and sex

During the mean follow-up of 4.3 ± 2.4 years, the primary endpoint occurred in 115 (47%) patients, which included 16 (14%) deaths (without AVR) and 99 (86%) AVRs. Additionally, 106 (43%) patients had a decline in functional status, defined as an increase in NYHA functional class (≥1 class) and/or a faster decline in DASI score (annualized score decline <-2 points/year, ie, median of the entire cohort) during follow-up.

Functional status decline was significantly associated with an increased rate of the composite of death or AVR ($P < 0.001$) (**Figure 3A**). When stratified by sex, there was a significant difference between groups ($P = 0.004$), with a higher rate of the composite of death or AVR in women and men having functional status decline (**Figure 3B**).

Incidence of the Composite of Death or AVR According to Functional Status Decline

Kaplan-Meier curves of the cumulative incidence of death from any cause or AVR according to functional status decline (A), and functional status decline and sex (B). Functional status decline was defined as an increase in NYHA functional class (≥1 class) and/or a faster decline in DASI score (annualized score decline <-2 points/year, ie, median of the entire cohort) during follow-up. AVR = aortic valve replacement; FS = functional status; other abbreviations as in **Figures 1** and **2**.

In univariable Cox analysis, the change in functional status was significantly associated with the primary endpoint (HR: 1.88; 95% CI: 1.29-2.74; $P = 0.001$) (**Table 4**). Similarly, when analyzed according to sex and

using men without functional status decline as a reference group, there was a significant association with the primary endpoint for women (HR: 1.93; 95% CI: 1.06-3.54; *P* = 0.03) and men (HR: 1.58; 95% CI: 1.02-2.45; *P* = 0.03) with functional status decline (**Table 4**). In multivariable Cox analyses, functional status decline remained significantly associated with the composite of death or AVR (HR: 2.13; 95% CI: 1.22-3.73; *P* = 0.008) (**Table 4**). Furthermore, after multivariable adjustment, functional status decline remained significantly associated with the composite of death or AVR both in women (HR: 2.25; 95% CI: 1.09-4.65; *P* = 0.02) and men (HR: 2.02; 95% CI: 1.07-3.83; *P* = 0.03) (**Table 4**). However, there was no significant difference between women and men with functional status decline in the adjusted composite risk of death or AVR (*P* = 0.76). The analyses without imputation are reported in the **Supplemental Results**.

Table 4Association of Functional Status Decline With the Primary Endpoint	**Risk of Death or Aortic Valve Replacement (nevents = 115)**			
	Univariable Analysis		**Multivariable Analysis**	
	HR (95% CI)	***P* Value**	**HR (95% CI)**	***P* Value**
Model n° 1				
Decline of functional status	**1.88 (1.29-2.74)**	**0.001**	**2.13 (1.22-3.73)**	**0.008**
Model n° 2				
Men	Reference		Reference	
No decline in functional status				
Women	0.67 (0.37-1.22)	0.19	0.95 (0.50-1.83)	0.89
No decline in functional				

Table 4Association of Functional Status Decline With the Primary Endpoint	**Risk of Death or Aortic Valve Replacement (nevents = 115)**			
	Univariable Analysis		**Multivariable Analysis**	
	HR (95% CI)	***P* Value**	**HR (95% CI)**	***P* Value**
status				
Men	**1.58 (1.02-2.45)**	**0.03**	**2.02 (1.07-3.83)**	**0.03**
Decline of functional status				
Women	**1.93 (1.06-3.54)**	**0.03**	**2.25 (1.09-4.65)**	**0.02**
Decline of functional status				

Multivariable *Model n°1* adjusted for age, sex, hypertension, diabetes, bicuspid aortic valve, LV mass index, E/e' ratio, peak aortic jet velocity (ie AS hemodynamic severity) as time-dependent, NYHA class as time-dependent, and DASI score as time-dependent.
Multivariable *Model n°2* same as multivariable *Model n°1* excluding sex. **Bold** values indicate significant association.
Abbreviations as in **Tables 1** and **2**.

Discussion

The main findings of this study are: 1) for the same degree of AS hemodynamic severity, and despite lower comorbidities at baseline, women have a worse functional status at baseline, which persisted during follow-up compared to men; 2) faster progression in AS severity was associated with a significant and rapid decline in functional status during follow-up, but with

a greater impact in women than in men; and 3) functional status decline during follow-up was strongly related to the incidence of death or AVR, with comparable effect in both women and men.

Decline in functional status during AS progression

The development, validation, and application of patient-centered outcomes, such as functional status, are key to improve the patient care journey for patients with valvular heart disease.**17** There are, however, very few studies that examined the changes in patient's functional/health status instruments during follow-up in patients with AS and these studies were generally focused on symptomatic patients with severe AS undergoing AVR.**18**,**19** Arnold et al**19** previously validated the Kansas City Cardiomyopathy Questionnaire—a disease-specific self-administered questionnaire—to monitor the functional status and quality of life of symptomatic patients with severe AS. The present study is the first to document that decline in functional status occurs early in the course of aortic valve disease and is, in large part, determined by the progression rate of AS hemodynamic severity. Indeed, hemodynamic progression of AS severity was strongly associated with the worsening of NYHA functional class and decline of DASI score, and these associations persisted after adjustment for age, sex, cardiovascular risk factors, and baseline AS severity. Although advanced age and comorbidities may contribute to the deterioration in patient's functional status during the course of AS, our findings suggest that the progression of AS hemodynamic severity is the main driver of this deterioration. Therefore, serial assessment of functional status may help to adjust periodic clinical and imaging follow-up of patients with initially mild-to-moderate AS and an increased risk of rapid disease progression.

Sex differences in decline of functional status

There is now compelling evidence supporting the presence of differences between women and men with respect to the fibro-calcific remodeling of the

aortic valve and LV remodeling response in AS.**20-24** While these differences may contribute to different clinical manifestations of AS, sex-specific deterioration of health status during disease progression has been largely unexplored. Prior studies have reported worse symptomatic status in women undergoing AVR compared to men.**4**,**25-27** However, women were also older, had more preoperative risk factors and more severe AS.**4**,**25-27** In the present study, based on observational and prospective longitudinal data, we found that for the same degree of AS hemodynamic severity, women presented with worse functional status at baseline compared to men. The sex-related difference in functional status was accentuated during follow-up. Singh et al **5** previously reported that, for a given degree of AS severity, women had earlier onset of symptoms than men but they did not assess quality of life. Our findings underscore the need to develop sex-specific criteria/parameters when interpreting the anatomical and functional consequences of AS progression.

In our study population, women were significantly younger than men at baseline. The younger age in women may explain the lower prevalence of comorbidities as well as the higher proportion of bicuspid aortic valve. Despite lower comorbidities, women had a similar degree of AS severity and LV filling pressure, but a greater degree of LV hypertrophy, which may have contributed to their functional status at baseline and throughout AS progression. We previously reported that female sex was an independent determinant of higher interstitial and replacement myocardial fibrosis.**23** In women with AS, the LV hypertrophic remodeling may contribute to impaired coronary microcirculation leading to repetitive myocardial ischemia and the development of myocardial fibrosis.**23** Therefore, myocardial fibrosis expansion, as a result of pressure overload and LV remodeling, could lead to more advanced LV diastolic dysfunction and thus more symptoms in women. On the other hand, other parameters, in addition to AS severity and LV consequences, may influence the decline in functional status of patients with AS. Indeed, perceived health and functional status may differ between women and men due to several other conditions including social and

cultural determinants.**28-30** This has been well illustrated in ischemic heart disease where poor social factors were associated with worse outcome in women.**31** Moreover, women typically have lower maximal oxygen consumption and shorter 6-minute walk test distances, independent of AS/symptoms, which may also explain the lower DASI score at baseline. However, in our study, women with faster AS progression experience a more rapid decline in functional status, even after adjustment for several confounding factors. Hence, these findings warrant further studies to better understand the sex-specific aspects of AS progression and management.

Prior studies have reported sex disparities in referral patterns for AVR.**4**,**26** Women with severe AS are less likely to be referred for surgical AVR or are referred at a more advanced stage of the disease versus men. This has been well documented in a recent large hospital network including more than 10,000 patients with severe AS.**32** Among patients with severe low-gradient AS, male sex was independently associated with higher likelihood of receiving AVR.**32** We have recently reported similar results in a large series of patients in whom women with severe low-gradient AS were less often referred to AVR, resulting in excess mortality among women.**7** Given that presence of severe AS and of symptoms are the primary triggers for intervention in AS, it is surprising to see that women are less often referred or referred later to AVR versus men. These findings may be related to the fact that both AS severity (probably because of high prevalence of low gradient AS) and of symptoms may be underestimated and/or misinterpreted to a larger extent in women vs men. However, these findings diverge from those of the present study, wherein women were not undertreated compared to men. The conflicting results are likely due to differences in the study population and endpoints. The present study included patients who were younger and at a less advanced disease stage, as evidenced by the significant age difference for women (>10 years), with yearly follow-up.

Future perspectives

AVR is up to now the only effective treatment for severe AS. However, several randomized trials have been initiated recently or will be launched in the near future to test whether pharmacotherapies are able to slow or block the progression of AS. For these trials, the primary outcomes are generally the progression of anatomic or hemodynamic severity of AS assessed by imaging. Recently, Lindman et al on behalf of the Heart Valve Collaboratory**33** emphasized the importance of also including patient-centered outcomes in the design of these trials. This recommendation is further buttressed by the present study (**Central Illustration**), which revealed an insidious decline in functional status parameters, affecting predominantly women in patients with initially mild or moderate AS.

Sex-Related Differences in the Decline of Functional Status in Patients With Mild-to-Moderate AS

Among patients with mild-to-moderate AS at baseline, women present with more symptoms and have worse decline in health status for similar AS hemodynamic progression rate.

Study Limitations

A causal relationship between faster AS progression rate and rapid decline in functional status could not be inferred. Notably, despite our effort to account for the effect of confounding factors, including underlying cardiovascular comorbidities and parameter of diastolic dysfunction, residual confounding effects may persist. Therefore, careful consideration is needed when interpreting these findings. However, compared to prior studies, we prospectively assessed patients' functional status on a yearly basis using well validated instruments. The DASI is not a cardiovascular disease (and so AS)-specific health status questionnaire and is limited by the lack of validated criteria to define the minimum decrease in DASI that can be considered clinically significant in terms of decline in functional status. Additionally, it is important to emphasize that the sex-specific

analysis, aimed at determining the prognostic value of functional status decline, serves primarily as hypothesis-generating.

Conclusions

In this prospective observational study of patients with mild-to-moderate AS at baseline, women with intermediate-to-fast hemodynamic progression rate of AS had a greater decline in functional status compared to men. The decline in functional status during follow-up was associated with a higher rate of the composite of death or AVR in both women and men. These findings lend support for the use of patient-centered endpoint to monitor AS disease progression and enhance risk stratification. However, they also highlight the need for sex-specific symptoms assessment tools in patient care.

10. Impact of Gender-Affirming Hormonal Therapy on Cardiovascular Risk Factors in Transgender Health: An Updated Meta-Analysis

Introduction

Transgender is a broad term encompassing individuals whose gender identity differs from the one assigned to them at birth.**1** Transgender individuals often go through gender-affirming hormone therapy (GAHT) or surgeries to achieve their desired sex appearance. Transgender men, also referred to as transmasculine (TM) use testosterone to obtain masculine features, while transgender women, also referred to as transfeminine (TF) utilize estrogen and antiandrogen hormones like spironolactone for feminization.**2**

The use and effects of GAHT have significantly been studied in premenopausal and postmenopausal women and males with hypogonadism. Supplementing androgen to hypogonadal males has been suggested to increase body muscle mass with positive effects on lipid and glycemic profiles or negative outcomes as reported by the World Health Organization

controlled trial on the use of combined contraceptive pills that increase the risk of the cardiovascular and thrombotic incident.**3-5** However, there are limited data regarding long-term clinical safety and outcome of hormonal therapy in transgender individuals.

Several studies on GAHT in healthy individuals suggest that estrogen and testosterone may elevate the risk of metabolic syndrome by inducing insulin resistance, dyslipidemia, and increased abdominal fat deposition, which leads to an increased risk of cardiovascular diseases (CVDs).**6-8** However, conflicting conclusions arise from other studies indicating the short-term safety of GAHT for transgender individuals.**9** The long-term cardiovascular safety of GAHT remains uncertain, primarily due to the current evidence relying heavily on expert opinion and retrospective case series, utilizing varied GAHT regimens, including older protocols, and occasionally lacking guidelines-based proactive risk management.

Therefore, we conducted a systematic review and meta-analysis of currently available literature to evaluate the influence of GAHT on the lipid profile and metabolic CVD risk factors that can impact cardiovascular outcomes in transgender individuals.

Methods

This systematic review was conducted by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The study eligibility criteria included populations that are either: 1) TF or TM individuals; 2) transgender individuals on GAHT; 3) age >12 years; 4) baseline reporting on metabolic and lipid profiles; and 5) outcomes reporting on changes in metabolic and lipid profiles before and after GAHT use. The exclusion criteria were age <12 years, no reporting of lipid profile or desired outcome, and patient pool not including TF or TM individuals.

A literature search was conducted on Medline/PubMed, Embase, and Cochrane for trials or observational studies with the abovementioned inclusion criteria using a systematic search strategy by PRISMA from

inception until January 2023. Search terms employed using Boolean Operators “OR” and “AND” among and between 2 subsets of keywords as “Transgender persons,” “transsexual persons” AND “sex hormones” OR “hyperlipidemias” OR “metabolome.”

Study selection

All available clinical trials or observational studies were evaluated. Two authors (S.R. and M.H.) independently reviewed the search results for studies that met the eligibility criteria. Any uncertainty regarding study selection was resolved with consensus with a third author (Y.S.).

In the first phase, titles and abstracts were screened and studies fulfilling the inclusion were selected for the second phase. In the second phase, we went through the full texts of the selected studies and further narrowed down our selection based on whether the studies reported items for data extraction.

Primary and secondary outcomes

The primary outcome of the study was the lipid profile of the TF and TM patients including triglyceride (TG) levels, total cholesterol (TC) levels, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Secondary outcomes included other factors that could have impacted CV outcomes including body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP).

Comparison of outcomes

We compared the change in the variables mentioned above from their baseline levels before the initiation of GAHT to their levels after the application of GAHT.

Data collection and statistical analysis

Statistical analysis was performed using the CRAN-R software. Data from each study included after the secondary screening were extracted in a Microsoft Excel sheet. Data elements collected were the number of TF and TM individuals, androgen or estrogen use, and mean age. Other characteristics collected were TG, TC levels, LDL, HDL, BMI, SBP, and DBP before and after GAHT.

A *meta-cont* module was used along with the inverse variance random effects model to calculate the pooled standard mean difference (SMD) with a probability value of $P < 0.05$ considered to be statistically significant. The "test for overall effect" was reported as a *z*-value corroborating the 95% CI's inference. Higgins I-squared (I2) was determined as a measure of statistical heterogeneity where values of ≤50% corresponded to low to moderate heterogeneity while values ≥75% indicated high heterogeneity.**10** For heterogeneity of more than 50%, we conducted a leave-one-out analysis to assess for studies contributing the most to heterogeneity using the meta-inf module in CRAN-R software. We also conducted a subgroup analysis based on follow-up duration. Four subgroups were identified: 1) up to 1 year; 2) 1 to 3 years; 3) 3 to 5 years; and 4) 5 to 10 years. The publication bias was depicted graphically and numerically as a forest plot and Begg's test.**11** The quality assessment of the included articles was performed using the Cochrane Risk of Bias (ROB) and Newcastle Ottawa Scale.**12-14**

Results

Our search identified 564 articles and following the removal of duplicates (n = 89), 475 records were screened in the first phase. Among them, 431 articles were removed. In the second phase, after removing duplicates and irrelevant studies, a total of 44 articles were selected for a full-length analysis. Of these, 24 studies were included in the final analysis which reported on our desired outcome. A total of 1241 TM and 992 TF individuals were included in our review (**Central Illustration**, **Figure 1**, **Supplemental S1**).

Impact of Gender-Affirming Hormonal Therapy on Cardiovascular Risk Factors in Transgender Health: An Updated Meta-Analysis

The outcomes of lipid profile comparison of pre- and post-GAHT use among transmasculine (TM) and transfeminine (TF) populations. Abbreviations as in **Figure 2**.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow of the Search Strategy for Systematic Review and Meta-Analysis

We included all GAHT therapies used for gender affirmation that were administered in various formulations such as oral, intramuscular (IM) injections, subcutaneous (SQ) injections, and gel. The GAHT utilized included combination of 17-β-estradiol and cyproterone acetate (oral), ethinyl estradiol (oral), goserelin acetate (SQ), and estradiol valerate (oral) for TF; and testosterone undecanoate (IM), lynestrenol (oral), testosterone cypionate (IM), testosterone enanthate (IM), testoviron depot (IM), anastrozole (oral), and testosterone gel for TM.

The mean follow-up duration for which studies were conducted (including pre- and post-GAHT therapy) was 27.69 months in TM patients and 39.23 months in TF patients. The mean SBP was 120.40 ± 11.31 mm Hg in TM patients and 119.60 ± 14.90 mm Hg in TF patients. The mean diastolic pressure was 73.96 ± 9.07 mm Hg in TM patients and 71.73 ± 10.40 mm Hg in TF patients. The mean age of the TM and TF cohorts was 28 years and 30 years, respectively. Baseline characteristics for TF and TM.

Table 3Pooled Outcomes of CV Risk Factors After GAHT Initiation in Transmasculine Individuals	**Standard Mean Difference (SMD)**	**95% CI**	***P* Value**	**I2**
LDL (mg/dL)	0.28	0.11-0.43	<0.01	61.1%
HDL (mg/dL)	−0.50	−0.67	<0.01	65.0%

Table 3Pooled Outcomes of CV Risk Factors After GAHT Initiation in Transmasculine Individuals	**Standard Mean Difference (SMD)**	**95% CI**	***P* Value**	**I2**
		to −0.32		
TG (mg/dL)	0.42	0.25-0.60	<0.01	62.8%
TC (mg/dL)	0.17	0.05-0.29	<0.01	30.5%
SBP (mm Hg)	−0.09	−0.61 to 0.42	0.72	89.4%
DBP (mm Hg)	−0.27	−0.76 to −0.21	0.27	88.9%
BMI (kg/m2)	0.24	0.11-0.38	<0.01	0.0%

CV = cardiovascular; DBP = diastolic blood pressure; SBP = systolic blood pressure;

Regarding secondary outcomes, BMI was significantly elevated when compared to the baseline (SMD: 0.24 kg/m2 [95% CI: 0.11-0.38] *P* = <0.01, I2 = 0.0%). However, no significant relationship between SBP (SMD: −0.09 mm Hg [95% CI: −0.61 to 0.42] *P* = 0.72, I2 = 89.4%) and DBP (SMD: −0.27 mm Hg [95% CI: −0.76 to 0.21] *P* = 0.27, I2 = 88.9%) was studied (**Supplemental S2**, **Table 3**).

Subgroup analysis

We further performed subgroup analysis to account for follow-up duration as it varied in various studies. Based on subgroup analysis for TM individuals, HDL levels showed significant reduction at up to 1 year, 1 to 3 years, and 3 to 5 years follow-up. However, a nonsignificant reduction was

found in 5 to 10 years follow-up. In the case of LDL, significant elevation was seen in up to 1 year and 3 to 5 years follow-up but nonsignificant elevation in 1 to 3 years and 5 to 10 years follow-up. In the case of TG, significant elevation was seen in up to 1 year, 1 to 3 years, and 5 to 10 years follow-up but nonsignificant elevation in 3 to 5 years follow-up. Regarding TC, significant elevation was seen in up to 1 year follow-up but nonsignificant elevation was observed in 1 to 3 years, 3 to 5 years, and 5 to 10 years follow-up. For BMI, up to 1-year follow-up showed significant elevation, however, 1 to 3 years and 3 to 5 years follow-up durations showed nonsignificant elevation. Regarding SBP and DBP, none of the subgroups showed any significant changes. These results are shown in **Supplemental S4A**.

TF individuals' primary and secondary outcomes

TF individuals showed a statistically significant increase in TG levels only when compared to the baseline levels (SMD: 0.64 mg/dL [95% CI: 0.01-1.26] *P* = 0.05, I2 = 91.6%). There was no statistically significant change in the rest of the primary outcomes including LDL (SMD: −0.05 mg/dL [95% CI: −0.56 to 0.46] *P* = 0.85, I2 = 91.6%), HDL (SMD: 0.25 mg/dL [95% CI: −0.74 to 1.23] *P* = 0.62, I2 = 97.6%), and TC (SMD: 0.005 mg/dL [95% CI: −0.18 to 0.18] *P* = 0.96, I2 = 67.2%) (**Figure 3**, **Table 4**).

Forest Plots for Primary Outcomes Comparing Lipid Profile Pre- and Post-GAHT Use Among Transfeminine (TF) Individuals

(A) Change in LDL levels pre-GAHT (baseline) and post-GAHT use. (B) Change in HDL levels pre-GAHT (baseline) and post-GAHT use. (C) Change in TG levels pre-GAHT (baseline) and post-GAHT use. (D) Change in TC levels pre-GAHT (baseline) and post-GAHT use. Abbreviations as in **Figure 2**.

Table 4Pooled Outcomes of CV Risk Factors After GAHT Initiation in Transfeminine Individuals	**Standard Mean Difference (SMD)**	**95% CI**	***P* Value**	**I2**
LDL (mg/dL)	−0.05	−0.56 to 0.46	0.85	91.6%
HDL (mg/dL)	0.25	−0.74 to 1.23	0.62	97.6%
TG (mg/dL)	0.64	0.01-1.27	0.05	91.6%
TC (mg/dL)	0.004	−0.18 to 0.18	0.96	67.2%
SBP (mm Hg)	−0.51	−1.44 to 0.43	0.29	96.6%
DBP (mm Hg)	−0.01	−0.81 to 0.79	0.97	88.1%
BMI (kg/m2)	0.38	−0.13 to 0.88	0.14	91.9%

Abbreviations as in **Tables 1** and **3**.

Regarding secondary outcomes, there was no statistically significant change observed in SBP when compared to the baseline (SMD: −0.51 mm Hg [95% CI: −1.44 to 0.43] *P* = 0.29, I2 = 96.6%), DBP (SMD: −0.01 mm Hg [95% CI: −0.81 to 0.78] *P* = 0.97, I2 = 88.1%), and BMI (SMD: 0.38 kg/m2 [95% CI: −0.13 to 0.88] *P* = 0.14, I2 = 91.9%) (**Supplemental S3**, **Table 4**).

Subgroup analysis

For TF individuals, the impact of follow-up duration on HDL levels did not show any significant change. LDL showed no significant changes in up to 1 year, 1 to 3 years, and 3 to 5 years follow-up, and only showed mild statistically significant reduction in 5 to 10 years follow-up. For TG, similarly up to 1 year, 1 to 3 years, and 3 to 5 years follow-up did not show any significant change, and only mild significant change was observed in 5 to 10 years follow-up. Regarding SBP, no subgroup showed any significant results. For DBP, only 1 to 3 years follow-up showed mild significant elevation. Up to 1 year follow-up showed nonsignificant elevation but 3 to 5 years and 5 to 10 year follow-up subgroups showed nonsignificant reduction. Thus, overall, the result is nonsignificant. Regarding BMI, all the subgroups showed nonsignificant elevation. The results of the subgroup analysis are shown in **Supplemental S4B**.

Publication bias

To ascertain the bias, we plotted funnel plots and then used Begg's test to assess for funnel plot asymmetry.**11** The plot's vertical axis uses standard error to estimate the sample size of the study, thereby, plotting larger studies at the top and smaller studies at the bottom. The horizontal spread depicts the power and effect sizes of the included studies. We did a numerical assessment of the funnel plot scatter using Begg's test that did not show any publication bias or small study effects (**Supplemental S5**).

Quality assessment

Bias assessment of randomized controlled trials was done using the Cochrane ROB tool.**12** In all of the intervention studies, there was no blinding because of the interventional nature of GAHT and parallel single-arm designs with no intergroup comparison. This raises a concern for selection bias. In most of the studies, data regarding matching are also not available. There is minimal risk of detection bias as all the outcomes were laboratory measures and robust data regarding laboratory methods are available. The risk of reporting bias was minimal due to adequate reporting

of outcomes. The overall risk of bias was high. The detailed ROB tool assessment of the intervention studies is given in **Supplemental S6**.

Quality assessment of non-randomized studies was assessed by the Newcastle-Ottawa Scale.**14** In all non-interventional studies, the quality of study population selection, comparability of the selected sample with the general population, and methods of measuring the outcome were assessed as depicted in **Supplemental S7**. The overall risk of bias for the observational studies included in the study was low.

Heterogeneity

In general, the high heterogeneity observed in the outcomes studied in our analysis is likely due to several factors. Firstly, it encompasses studies utilizing diverse GAHT approaches. Secondly, most of the studies in our analysis exhibited notable selection bias, both in non-randomized observational studies and even in randomized controlled trials, contributing to a high risk of overall bias. Thirdly, such pronounced heterogeneity may be explained by sampling bias.

To further assess heterogeneity, we conducted a leave-one-out analysis. In TM individuals, the outcomes with >50% heterogeneity were HDL, LDL, TG, SBP, and DBP. For HDL, almost all studies contributed equally to heterogeneity except Liu et al.**29** Omitting this study resulted in an overall pooled HDL of −0.55 mg/dL (95% CI: −0.7 to −0.40; $P < 0.01$) compared to the baseline and a decrease in I2 value to 50%. For LDL, the study contributing the most to heterogeneity was again Liu et al.**29** Omitting this study led to a pooled LDL increase of 0.35 mg/dL (95% CI: 0.24 to 0.49; $P < 0.01$) from baseline and a resultant heterogeneity of 31%. The rest of the studies contributed equally to heterogeneity. For TG, all the studies contributed to heterogeneity except Wierckx et al.**37** Omitting this study led

to a total heterogeneity of 51% and a pooled increase in TG from a baseline of 0.389 mg/dL (95% CI: 0.24-0.53; *P* < 0.01). Regarding SBP, the study contributing to heterogeneity was again Liu et al**29** while all other studies contributed equally to heterogeneity. Omitting Liu et al**29** decreased heterogeneity to 68% and a change in SBP of 0.12 mm Hg (95% CI: −0.15 to 0.37; *P* = 0.38) from baseline. Regarding DBP, all studies contributed equally to heterogeneity except Liu et al.**29** Omitting this study led to a decrease in heterogeneity to 50% and a final pooled change in DBP of −0.02 mm Hg (95% CI: −0.23 to 0.19; *P* = 0.85) from baseline. **Supplemental S8A**.

In TF individuals, regarding HDL, all studies contributed equally to heterogeneity. Regarding LDL, Liu et al**29** contributed most to heterogeneity. Omitting it led to a decrease in heterogeneity to 72% and a pooled LDL difference of −0.18 mg/dL (95% CI: −0.43 to 0.06; *P* = 0.15) from baseline. Regarding TC, Cocchetti et al**20** and Wierckx et al**37** contributed the most to heterogeneity. Removing Cocchetti et al decreased heterogeneity to 51% with pooled TC of 0.06 mg/dL (95% CI: -0.11 to 0.23; *P* = 0.48) as compared to baseline; while removing Wierckx et al decreased heterogeneity to 54% with pooled TC of 0.07 mg/dL (95% CI: -0.09 to 0.22; *P* = 0.40) from baseline. Regarding TG, all studies contributed almost equally to heterogeneity. Regarding SBP, Liu et al**29** contributed the most to heterogeneity. Its omission led to a decreased heterogeneity to 90% with a pooled SBP difference of −0.08 mm Hg (95% CI: -0.60 to 0.44; *P* = 0.77) compared to baseline. For DBP, Deutsch et al**21** contributed the most to heterogeneity. Its omission led to a decrease in I2 levels to 68% and pooled DBP changed to about 0.33 mm Hg (95% CI: 0.08-0.05; *P* = 0.01). Here omission of the most heterogeneous study changed the results to a statistically significant increase in DBP as compared to baseline. Deutsch et al had a short follow-up duration, which likely skewed the overall effect and contributed to the normalization of DBP. Also, medication adherence was not consistently tracked among most patients, a limitation acknowledged within the study. Regarding BMI, Mueller et al**31** was the most heterogeneous study and its omission led to a decrease in I2 value to 57%

and pooled BMI differed by 0.20 kg/m2 (95% CI: −0.04 to 0.43; *P* = 0.10) from baseline **Supplemental S8B**.

Compared to other studies, Liu et al**29** differed significantly in methodology, potentially contributing to high heterogeneity. While other studies included some patients with baseline dyslipidemia, Liu et al**29** opted to exclude individuals with dyslipidemia. Follow-up duration was variable in Liu et al**29** with some participants monitored at 3 months, others at 6 months, and some for even longer periods. Moreover, loss to follow-up was high as compared to the other studies, also contributing to high heterogeneity.

Discussion

We performed a systematic review and meta-analysis to outline the effect of GAHT on lipid profile in transgender patients. Our results show a statistically significant increase in TG levels in transgender women with no significant changes in TC, LDL, HDL levels, or changes in SBP and DBP when compared to the baseline levels. On the other hand, transgender men had a statistically significant increase in TG, LDL, and TC levels and a decrease in HDL levels with no significant changes in SBP or DBP as compared to the baseline levels.

The primary class of estrogen (17-β estradiol) and ethinyl estradiol were the most commonly used regimens given to transgender women in our selected studies. The amount of estrogen used in transgender individuals is much higher than in women on hormone replacement therapy or oral contraceptive pills (5 mg estradiol/24 h compared to 100 µg estradiol/24 h) which could explain the variability of the results on lipid profiles.**39** For instance, in a study by Walsh et al postmenopausal women on low-dose estrogen (1.25 mg/day) have favorable outcomes in lipid profile as there was a 19% increase in HDL and an 18% reduction in LDL level, which could protect women against atherosclerosis.**40** In addition to that, the mode of delivery may be another contributing factor, as transdermal 17-estradiol is the safest method of administration in terms of thromboembolic events,

which might have mitigated effects on lipid profiles in comparison to the oral form.**7**,**41** On the other hand, studies by New et al**42** found an increased level of HDL and TC and lower LDL in transgender women compared to men who are not on treatment which correlates with our study findings.

Testosterone therapy in eugonadal cisgender men might increase TG levels and reduce TC, LDL, and HDL levels in cisgender eugonadal men. On the other hand, androgen deficiency is linked with an increase in TG, TC, LDL, and HDL levels.**43**,**44** However, the effect of testosterone on lipid profile in transgender men in our meta-analysis shows a significant increase in TG, LDL, and TC levels and a decrease in HDL levels. Our results correlate with a large retrospective study performed on 89 transgender men individuals who had GAHT and reported that TGs, TC, and LDL levels were increased, while HDL was decreased.**45**

GAHT can adversely affect lipid profiles, potentially increasing the risk of myocardial infarction and ischemic stroke. This risk is attributed to alterations in cholesterol levels resulting from hormone therapy. Moreover, GAHT has been associated with an increased risk of venous thromboembolism (VTE).**46-48** The use of oral ethinyl estradiol in transgender women carries a significant 20-fold increased risk of spontaneous VTE.**49** Notably, all VTE cases occurred in patients using oral ethinyl estradiol, except for a single case using transdermal 17-β-estradiol in the latter study.**45** Estradiol valerate is a novel estrogen with fewer side effects than ethinyl estradiol and is now the most commonly prescribed form of estrogen in transgender women.**50**

Numerous studies have explored the metabolic impacts of GAHT in transgender individuals, but findings are frequently conflicting and inconclusive. This is largely due to the observational and retrospective nature of the studies, which involve populations with varied hormone regimens, often without medical supervision.**51-54** While our analysis suggests an association of GAHT with dyslipidemia, which could potentially indicate a higher cardiovascular mortality risk, it remains uncertain whether

transgender individuals have a higher cardiovascular mortality rate compared to the general population.**55**

A previous meta-analysis conducted by Elamin et al in 2010 concluded that current level of evidence is of low quality, characterized by significant imprecision and heterogeneity.**56** Similarly, previous systematic reviews suggest that the current data on GAHT in transgender patients are limited and of low quality.**22**,**52**,**57**,**58**

In summary, our meta-analysis reveals statistically significant changes in lipid profiles among transgender individuals undergoing GAHT. However, the clinical implications of GAHT on lipid profiles remain unclear. Current evidence is insufficient to draw definitive conclusions about its impact. Additional research is essential to determine if these changes affect cardiovascular morbidity and mortality. Long-term studies with extended follow-up are crucial to gain a comprehensive understanding of these potential impacts.

Study Limitations

We did not have a long-term follow-up of data and CVD data available including myocardial infarction and major adverse cardiovascular events due to dyslipidemia in the transgender population. Individual genetic, dietary, and lifestyle factors can act as confounders and effect modifiers that can alter the results. The study includes data sets from older studies that used ethinyl estradiol as part of GAHT. Ethinyl estradiol is known to be pro-thrombotic, which is why it is no longer used in GAHT. Limited evidence from small studies with diverse hormone treatments and follow-up durations makes drawing definitive conclusions challenging.

Because of high heterogeneity, even statistically significant results do not translate into clinical significance. A similar observation was made by a meta-analysis done 14 years ago.**56** The available evidence regarding the effects of GAHT in TM and TF individuals remains low in quality with a lot of imprecisions precluding its clinical use.

Conclusions

Our meta-analysis found that the initiative of GAHT in TM individuals was associated with increases in LDL, TGs, TC, and a decrease in HDL levels. In TF individuals, GAHT was associated with an increase in TG levels only. There was no impact on blood pressure or BMI. Whether these changes in lipids after GAHT translate into unfavorable clinical outcomes is yet to be determined.

11. The Pandora's Box of Hypertensive Heart Disease in Women

Introduction

Recently, there has been significant advancement in the recognition of sex and gender-based differences in cardiovascular health and disease. However, while hypertension remains the most common medical diagnosis and modifiable cardiovascular risk factor regardless of sex, a sex- and gender-based approach to diagnosis and management of hypertension has not been explored.**1-4** Of note, although the terms sex and gender are used interchangeably in the literature, it should be recognized that sex is a biologic construct, while gender is a social construct; analysis and reporting frequently blur these definitions, as exemplified in this editorial, due to imprecision of source documents.

Autonomic and hormonal function are key contributors to the regulation of blood pressure (BP).**3**,**4** Females experience unique events over the course of their lifespan related to reproductive biology including menarche and menstruation, pregnancy, and menopause. After the onset of menopause, hypertension is more prevalent in females than males.**3**,**4** Despite this, underdiagnosis of hypertension is more common in women than men, and when women are treated with antihypertensive medications, it has been found to be less well controlled than men.**3**,**4** Additionally, women have a unique profile when it comes to efficacy and adverse effects of some

antihypertensive medical therapies.**4** There is also a sex-specific cardiac response to chronic hypertension and pressure overload.**4** It was initially demonstrated within the analysis of the Framingham Heart Study that women with systolic hypertension experience higher rates of hypertensive left ventricular concentric remodeling and hypertrophy,**5** a finding has since been corroborated in several observational studies.**6-8** Once established, hypertensive left ventricular hypertrophy (LVH) is less modifiable by antihypertensive treatment in females than males.**8** Although the overall risk for cardiovascular disease is lower in premenopausal women, this protection is lost after the onset of menopause. Interestingly, it has been shown that the presence of LVH in hypertension offsets the female sex-protection in cardiovascular risk, such that among hypertensive subjects with LVH, both sexes have comparable cardiovascular risk.**9** It has also been observed that although healthy young women have lower BP than men at similar age, they experience a steeper increase in BP from the third decade of life onward, and women with hypertension more often develop heart failure with preserved ejection fraction and atrial fibrillation, whereas men more often develop acute myocardial infarction and heart failure with reduced ejection fraction.**4**,**9**,**10** While sex-related differences in hypertension and left ventricular geometry have been clearly demonstrated,**5-8** to date these observations have not translated into mechanistic understandings for these differences, potentially leading to the creation of sex-specific diagnosis or management guidelines in clinical practice. This is primarily due to a lack of sex- and gender-specific analysis and reporting in large clinical trials on treatment and outcomes in hypertension.

In this issue of *JACC: Advances,* Canciello et al**11** add to the substantial data supporting sex-based differences in hypertensive heart disease by demonstrating the longitudinal impact of hypertension on ventricular morphology and remodeling. This study reports on a post-hoc sex-disaggregated analysis of echocardiograms from 6,427 patients (43% female) in the Campania Salute Network observational registry of hypertensive

patients and found over twice the rate of left ventricular remodeling and hypertrophy in females at both baseline and follow-up (mean of 6.1 years) when compared to males. These increased rates of abnormal geometry were found despite exclusion of patients with established cardiovascular disease or significant chronic kidney disease. Female sex was independently associated with abnormal left ventricular geometry in multivariate analysis with an odds ratio of 2.36 (95% CI: 2.12-2.62; $P < 0.001$).

An unexpected result was that the majority of females with abnormal geometry had eccentric hypertrophy, a finding previously thought to be more common in males.**12** No clear hypothesis was given for this observation, but it is possible that this may represent a longer duration of undertreated hypertension, and an associated increased predisposition to subclinical microvascular coronary artery disease in this female population, leading to more extensive fibrotic changes and eccentric dilation. In a recent study evaluating altered left ventricular geometry using cardiac magnetic resonance imaging and adjusted for epicardial coronary artery disease, it was shown that concentric hypertrophy was associated with increased all-cause mortality in both sexes, while eccentric hypertrophy was associated with increased all-cause mortality only in females.**12** Bairey Merz et al**13** pointed to the disproportionate burden of microvascular coronary dysfunction in females as a possible explanation for the increased adverse mortality.

Although observational studies of this nature cannot determine causal relationships, Canciello et al**11** report findings that are in keeping with previous similar cross-sectional studies and uniquely add to this growing body of information by providing longitudinal evidence for persistent sex disparities over time, shedding light on the prognostic importance of early identification of these sex-specific morphologic changes in response to altered physiology using the readily accessible tool of echocardiography. In addition to LVH, which has been considered the cardinal echocardiographic biomarker of pressure overload and associated cardiac damage, strain assessment of the left ventricle and left atrium are emerging areas of

exploration providing more sensitive markers of hypertensive changes preceding chamber enlargement or hypertrophy and may eventually play a greater role in earlier recognition of cardiac alterations and response to antihypertensive treatment.**14** Sex-differences have been identified in both ventricular and atrial strain, and the establishment of sex-specific strain reference values would be an essential step for unlocking strain assessments as potential tools aiding in mechanistic understanding and management.**15**,**16**

Limitations to retrospective analysis of observational data are acknowledged by the group, including the undefined role of potential underlying subclinical coronary artery disease and lack of detail regarding individual antihypertensive therapies. In addition, there is no data addressing the potential for associations with cardio-obstetric sex-specific cardiovascular risk factors such as hypertensive pregnancy disorders (preeclampsia, eclampsia), polycystic ovary syndrome, menopausal status, and hormonal drug therapies.

In summary, this latest observational study by Canciello et al**11** confirms sex disparities in the physiologic response to hypertension adding to the growing body of research demonstrating sex-specific differences of hypertensive heart disease and prognostic implications of these differences, and in so doing raises many questions that urgently require answers. Why do female hypertensive patients exhibit a higher propensity for left ventricular remodeling than their male counterparts? Is eccentric hypertrophy truly more prevalent in females? If so, what is the adaptive impact and association with increased clinical prevalence of coronary microvascular dysfunction and heart failure with preserved ejection fraction in females? What new pharmacologic strategies could be indicated? There is a clear need to better understand the underlying mechanisms of these sex differences in adaptive ventricular geometry in order to develop optimal sex-specific diagnostic and prognostic strategies to guide the optimal management of hypertension in women. Moreover, this work underscores the importance of considering sex- and gender-specific factors in risk

assessment and management strategies and demonstrates that analysis of data through a sex-specific lens is essential to our understanding of cardiovascular pathophysiology. Integrating sex-specific risk factors into risk stratification models is a crucial step toward more tailored and effective clinical interventions

12. Sex-Related Differences in Left Ventricular Geometry Patterns in Patients With Arterial Hypertension

Introduction

Structural and functional characteristics of the left ventricle (LV) are highly correlated in the pathophysiology of arterial hypertension.**1** The systemic hemodynamic profile often parallels the changes in LV geometry, with concentric remodeling and LV hypertrophy (LVH) associated with a higher peripheral resistance. Conversely, a supernormal cardiac index is often observed in patients exhibiting eccentric LV hypertrophy, with a low-to-normal range seen in cases of concentric LV remodeling.**2** Despite extensive investigation on the relationship between arterial hypertension and LV remodeling,**3** the impact of sex on this process remains underexplored.**4** Data evaluating the role of sex on basal LV geometry, subsequent changes over time, and the mediating effects of treatment are scarce. Yet, emerging evidence highlights that sex-based differences significantly influence not only the prevalence and clinical presentation of hypertension but also impacts on morphofunctional cardiac adaptations in response to elevated blood pressure (BP).**4** Therefore, identifying sex-specific differences in LV geometry is key for tailoring effective management strategies for arterial hypertension. Against this backdrop, we analyzed LV geometry patterns at baseline and their evolution during long-term follow-up within the Campania Salute Network registry, a large, prospective, observational study of patients with arterial hypertension.

Methods

The design and methodology of the Campania Salute Network registry (**NCT02211365**) have been described previously.**5-7** Briefly, the Campania Salute Network is an open registry collecting information from general practitioners and community hospitals in the five districts of the Campania Region in Southern Italy, networked with the Hypertension Research Center of the Federico II University Hospital in Naples. All participants were referred to the center for baseline work-up screening and echocardiogram.**5**,**8** The Campania Salute Network was approved by the institutional ethics committee, and a signed informed consent was obtained from all participants.

Definitions

Hypertension was diagnosed when office systolic BP readings were ≥140 mm Hg and/or diastolic BP readings were ≥90 mm Hg, or when antihypertensive therapy was prescribed.**9** Systolic and diastolic BP was measured after 5 minutes resting in the sitting position by a trained physician or nurse, according to current guidelines and standard procedures of Campania Salute Network.**10** Follow-up systolic and diastolic BP were also considered as the average office BP recorded during all control visits.**11** Diabetes was classified following the 2007 American Diabetes Association criteria (fasting plasma glucose >125 mg/dL or antidiabetic treatment).**12** Obesity was identified as a body mass index ≥30 kg/m2.**12** The glomerular filtration rate was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula.**11**

Echocardiographic evaluation

Echocardiographic examinations were performed at our Hypertension Center, and quality-controlled validation was performed for each exam executed, as previously reported in detail.**13** Echocardiograms recorded in our

hypertension center using commercial machines and a standardized protocol were digitally mastered and read offline by one expert reader (ASE III level) under the supervision of a senior faculty member (ASE III level).**13** All measurements were made following American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations.**14**,**15**

LV mass was estimated using a necropsy-validated formula, with the results indexed to body surface area (LV mass index).**15** A LV mass index >115 g/m2 in males and >95 g/m2 in females identified LV hypertrophy (LVH).**9**,**16** A relative wall thickness (RWT) ≥0.43 defined LV concentric geometry **9**,**17** in absence of LVH. LVH in presence of a concentric geometry was defined as concentric LVH, whereas a RWT <0.43 was categorized as eccentric. Concentric geometry, or LVH, either concentric or eccentric, identified LV remodeling. LV volumes were estimated from linear measures of LV diameters by the *z*-derived method and used to compute the LV ejection fraction.**18** We considered two echocardiograms for each patient: that at baseline and the last available one, which was considered at follow-up.

Statistical analysis

Data are expressed as mean ± SD for continuous variables and as absolute frequency and percentage for categorical variables. The chi-square test was used to compare categorical variables with the Monte Carlo simulation to obtain exact *P* values. We used the 4-tier classification of LV geometry as suggested by recommendation: normal, concentric remodeling, eccentric, and concentric LVH.**9**,**16**,**17**

Firstly, associations between the covariates and the LV geometry pattern were assessed using crude and adjusted ordinal logistic regressions both at baseline (considering only baseline variable measures) and at the end of the follow-up period (considering only measures at follow-up). The results of the ordinal logistic regression models are reported as crude and adjusted ORs,

which are to be interpreted as the estimated risk (by covariate) of changing the current LV geometry up by 1 tier. To investigate the determinants of the longitudinal changes in the LV geometry pattern, a multiple ordinal mixed-effect regression model with logit link was adopted, considering the patient's ID as random-effect and follow-up time as a random-effects offset. Time considered as indexes for baseline and follow-up was also added as fixed effect. We have also run an additional analysis, dichotomizing the LV geometry pattern variable into normal and pathological pattern. The variables associated with a pathological LV pattern were evaluated using crude and adjusted logistic regression. As previously reported,**13** the study accounts for antihypertensive therapy by calculating the total number of medications, including antirenin-angiotensin system (angiotensin converting enzyme inhibitors and AT1 receptor antagonists), calcium channel blockers, beta-blockers, and diuretics, at each visit. This total is reported based on the frequency of prescriptions during follow-up. If a medication was prescribed for more than 50% of control visits for a patient, it was included as a covariate in the follow-up multivariate analysis. To create a single variable representing overall antihypertensive therapy, the study adds up all the medications prescribed more than 50% of the time. This cumulative count is used as a continuous variable called "total therapy." This variable quantifies the overall intensity of antihypertensive treatment each patient is receiving.

Patients with preserved normal geometry were the reference group in this analysis.

A two-tailed *P* value <0.05 was considered statistically significant in all analyses. Data were analyzed using SPSS (version 26.0, SPSS) and R Statistical Software (version 4.3.0).

Results

Between 1990 and 2014, a total of 14,161 hypertensive patients were included in the Campania Salute Network registry. We excluded patients

under 18 years of age (N = 106), with prevalent cardiovascular disease (myocardial infarction, coronary revascularization, stroke, transient ischemic attack, valvular heart disease, N = 284), LV ejection fraction <50% (N = 1,588), chronic kidney disease stage >III (N = 2,198), incident myocardial infarction (N = 51), incomplete echocardiographic data at baseline and/or at follow-up (N = 452), and patients with less than 1-year follow-up (N = 3,055). Thus, the final population was of 6,427 patients, with a mean age of 53 ± 11 years, of which 2,778 (43%) were females. Mean follow-up time was not statistically different between the 2 sexes, with a mean of 6.2 ± 4.4 years for males and 5.8 ± 4.2 for females. Intraobserver and interobserver variability was assessed by the repeatability coefficient, determined as 1.96 × SD of the absolute value of the differences.**19** The repeatability coefficient was assessed for the variables enabling the measurement of LVH and of RWT: interventricular LV septum, posterior wall, and end-diastolic diameter. The intraobserver and interobserver repeatability coefficients were 0.4 and 0.9 mm for interventricular septum, 0.7 and 1.0 mm for posterior wall, and 1.1 and 1.8 mm for end diastolic diameter, respectively. **Table 1** shows the baseline characteristics of the study population stratified by sex. In comparison to males, female patients were older, had a longer history of hypertension, and had a higher prevalence of obesity. Additionally, females had a higher systolic and diastolic BP, heart rate, LV ejection fraction, and smaller left atrial and LV end-diastolic diameters. As shown in **Table 1** and the **Central Illustration**, a normal geometric pattern was less common in female than in male patients (50% vs 72%, $P < 0.001$); concentric remodeling was present in few patients and was less common in females than in males (3% vs 5%, $P < 0.001$). LVH was more prevalent among females (47% vs 23%, $P < 0.001$), with females having a higher rate of eccentric LVH (40% vs 18%, $P < 0.001$) and a higher prevalence of concentric LV hypertrophy than males (7% vs 5%, $P < 0.001$) (**Table 1**, **Central Illustration**).

Table 1Baseline Clinical and Echocardiographic Characteristics of the Population Stratified by Sex	**Men (n = 3,649)**	**Female (n = 2,778)**	**Difference**	**95% CI**
Age (y)	52 ± 11	55 ± 11	−0.24	−0.29 to −0.19
Years of hypertension	5.7 ± 6.5	6.7 ± 7.3	−0.15	−0.20 to −0.10
Obesity (%)	864 (24%)	724 (26%)	−2.4%	−4.6% to −0.22%
Diabetes (%)	343 (9%)	244 (9%)	0.62%	−0.83% to 2.1%
Dyslipidemia	2,933 (81%)	2,381 (86%)	−5.3%	−7.1% to −3.4%
Systolic blood pressure (mm Hg)	141 ± 17	144 ± 19	−0.13	−0.18 to −0.08
Diastolic blood pressure (mm Hg)	90 ± 11	88 ± 11	0.11	0.06-0.16
Heart rate (bpm)	74 ± 11	75 ± 12	−0.12	−0.17 to −0.07
Left atrial diameter (cm)	3.8 ± 0.3	3.6 ± 0.4	0.061	0.06-0.07
Left ventricular end diastolic diameter (cm)	5.1 ± 0.3	4.8 ± 0.3	1.1	1.0-1.3
Left ventricular ejection fraction (%)	66 ± 4	67 ± 4	−0.20	−0.25 to −0.15
Relative wall thickness	0.38 ± 0.04	0.38 ± 0.04	−0.07	−0.12 to −0.02
Left ventricular mass (g/m2)	105 ± 18	95 ± 15	0.55	0.49-0.60

Table 1 Baseline Clinical and Echocardiographic Characteristics of the Population Stratified by Sex	**Men (n = 3,649)**	**Female (n = 2,778)**	**Difference**	**95% CI**
Left ventricular geometry patterns				
Normal left ventricular pattern	72%	50%	22%	20%-25%
Concentric left ventricular pattern	5%	3%	1.8%	0.85%-2.8%
Eccentric left ventricular hypertrophy	18%	40%	−22%	−24% to −19%
Concentric left ventricular hypertrophy	5%	7%	−2.5%	−3.8% to −1.3%

Values are mean ± SD or n (%) unless indicated otherwise. Difference expressed as standardized mean difference for quantitative variables and as risk difference for proportions.

n

Sex-Related Differences in Left Ventricular Geometry Patterns in Patients With Arterial Hypertension

(Upper panel) Main methods of the study; (lower panels) main results of the study. LVH = left ventricular hypertrophy.

At multivariable analysis conducted at baseline (**Table 2**), female sex was independently associated with abnormal LV geometry (OR: 2.36; 95% CI: 2.12-2.62; $P < 0.001$). Other significant determinants included age, duration of hypertension, systolic BP, obesity, and diabetes. **Figure 1** illustrates the age and sex-stratified adjusted estimated probability densities for each LV geometric pattern. The analysis showed that with each incremental year of

age, the risk of an abnormal pattern increased by 4%, with females having a 2.36 times higher risk than males.

Table 2Determinants of Abnormal Left Ventricular Geometry at Baseline (Concentric Remodeling or Eccentric and Concentric Left Ventricular Hypertrophy): Univariable and Multivariable Logistic Regression Models	**OR**	**95% CI**	***P* Value**	**Adjusted OR**	**95% CI**	***P* Value**
Age (y)	1.05	1.05-1.06	<0.001	1.04	1.04-1.05	<0.001
Female	2.59	2.35-2.87	<0.001	2.36	2.12-2.62	<0.001
Duration of hypertension (y)	1.05	1.05-1.06	<0.001	1.02	1.01-1.03	<0.001
Systolic BP (mm Hg)	1.02	1.02-1.03	<0.001	1.02	1.01-1.02	<0.001
Diastolic BP (mm Hg)	1.01	1.00-1.01	<0.001	1.00	1.00-1.01	0.306
Obesity	1.45	1.29-1.62	<0.001	1.35	1.20-1.52	<0.001
Diabetes	1.81	1.53-2.12	<0.001	1.23	1.04-1.46	0.018

Variables statistically significant at univariable were included in the multivariable logistic regression model.

BP = blood pressure.

Effect Plot of the Adjusted Probability of Showing Each Left Ventricular Geometry Pattern by Sex and Age Estimated With Ordinal Logistic Regression

LV = left ventricle; LVH = left ventricular hypertrophy.

At long-term follow-up of 6.1 years (IQR: 2.8-8.6 years), we observed an increased proportion of patients with abnormal LV geometric patterns in both sexes (**Table 3**, **Central Illustration**). Specifically, concentric LVH increased mostly in females than in males (**Table 3**, **Central Illustration**). During follow-up, systolic and diastolic BP were different between males and females, with females having lower diastolic (83 ± 7 mm Hg vs 85 ± 7 mm Hg, respectively, $P < 0.001$) and higher systolic BP than men (138 ± 13 mm Hg vs 136 ± 11 mm Hg, respectively, $P < 0.001$). In addition, while the prescription of only 1 antihypertensive drug was similar among females than males (33% vs 34%, respectively, $P = 0.195$), the administration of more than two antihypertensive medications was more common in females than in males during follow-up (19% vs 16%, respectively, $P = 0.003$). **Table 4** reports the results of the longitudinal model, which confirms a significant effect of age (24% higher risk per each increasing year of age) and a significant higher risk in females (250%) of progressing to a pathological LV geometry. Other significant covariates were duration of hypertension, abnormal BP control, and total therapy. Additionally, time was an independent predictor of progression. The full model outputs with R call and code for the models shown in **Tables 3** and **4** and in the **Supplemental Material**. **Table 5** outlines the variables associated with worsening patterns over time. Aging, obesity, diabetic status, and female sex together with a longer history of hypertension, poor BP control, and treatment with more antihypertensive drugs during follow-up were associated with worsening patterns at long-term follow-up. Alluvial plots of the individual changes in LV geometry pattern from baseline to follow-up in males and females are

reported in **Figure 2**. **Central Illustration** reports the main methods and results of our study.

Table 3Univariable and Multivariable Ordinal Logistic Regression Model to Investigate the Determinants of Pathological LV Geometry at Follow-Up	**OR**	**95% CI**	***P* Value**	**Adjusted OR**	**95% CI**	***P* Value**
Age (y)	1.06	1.05-1.06	<0.001	1.04	1.04-1.05	<0.001
Female vs male	2.69	2.44-2.96	<0.001	2.50	2.25-2.77	<0.001
Duration of hypertension (y)	1.05	1.05-1.06	<0.001	1.01	1.00-1.02	0.003
Normal vs abnormal BP control for more than 50% of visits during follow-up	0.50	0.46-0.56	<0.001	0.58	0.52-0.64	<0.001
Obesity at follow-up						
Never obese	–	–	–	–	–	–
Ex obese	1.77	1.44-2.18	<0.001	1.69	1.35-2.10	<0.001
New obese	1.12	0.91-1.38	0.266	1.19	0.96-1.48	0.112
Ever obese	1.56	1.38-1.76	<0.001	1.41	1.24-1.61	<0.001
Diabetes at follow-up						
Never diabetes	–	–	–	–	–	–
New diabetes	1.44	1.21-1.71	<0.001	1.16	0.97-1.39	0.099

Table 3Univariable and Multivariable Ordinal Logistic Regression Model to Investigate the Determinants of Pathological LV Geometry at Follow-Up	**OR**	**95% CI**	***P* Value**	**Adjusted OR**	**95% CI**	***P* Value**
Ever diabetes	2.16	1.83-2.55	<0.001	1.40	1.17-1.67	<0.001
Follow-up years	1.03	1.02-1.04	<0.001	1.06	1.04-1.07	<0.001
Total therapy						
No therapy	–	–	–	–	–	–
1 drug	1.29	1.09-1.52	0.002	1.18	0.99-1.41	0.061
2 drugs	1.90	1.62-2.23	<0.001	1.50	1.26-1.79	<0.001
3 drugs	2.73	2.27-3.29	<0.001	1.79	1.46-2.19	<0.001
4 drugs or more	5.03	3.79-6.68	<0.001	2.48	1.83-3.36	<0.001

BP = blood pressure; LV = left ventricular.

Table 4Longitudinal Model of Progressing to a Pathological LV Remodeling	**Adjusted OR**	**95% CI**	***P* Value**
Age (y)	1.24	1.21-1.26	<0.001
Female vs male	2.50	2.25-2.77	<0.001
Duration of hypertension (y)	1.04	1.00-1.07	0.026

Table 4Longitudinal Model of Progressing to a Pathological LV Remodeling	**Adjusted OR**	**95% CI**	***P* Value**
Normal vs abnormal BP control for more than 50% of visits during follow-up	0.08	0.05-0.12	<0.001
Obesity vs no obesity (longitudinal measure)	1.10	0.83-1.45	0.508
Diabetes vs no diabetes (longitudinal measure)	1.23	0.88-1.72	0.229
Total therapy	1.80	1.45-2.23	<0.001
Time (follow-up vs baseline effect)	2.09	1.86-2.36	<0.001

Abbreviations as in **Table 3**.

Table 5Univariable and Multivariable Binary Logistic Regression Model to Investigate the Determinants of Normal vs Pathological LV Pattern at Follow-Up	**OR**	**95% CI**	***P* Value**	**Adjusted OR**	**95% CI**	***P* Value**
Age (y)	1.06	1.05-1.06	<0.001	1.04	1.04-1.05	<0.001
Female vs male	2.62	2.36-2.90	<0.001	2.50	2.24-2.79	<0.001
Duration of hypertension (y)	1.05	1.05-1.06	<0.001	1.01	1.00-1.02	0.006
Abnormal vs normal BP control for more than 50% of visits during follow-up	0.53	0.47-0.58	<0.001	0.58	0.52-0.65	<0.001

Table 5Univariable and Multivariable Binary Logistic Regression Model to Investigate the Determinants of Normal vs Pathological LV Pattern at Follow-Up	**OR**	**95% CI**	***P* Value**	**Adjusted OR**	**95% CI**	***P* Value**
Obesity at follow-up						
Never obesity	–	-	–	–	–	–
Ex obese	1.76	1.41-2.21	<0.001	1.74	1.36-2.22	<0.001
New obese	1.10	0.89-1.35	0.393	1.14	0.91-1.44	0.256
Ever obese	1.56	1.38-1.77	<0.001	1.43	1.25-1.65	<0.001
Diabetes at follow-up						
Never diabetes	–	–	–	–	–	–
New diabetes	1.40	1.17-1.67	<0.001	1.14	0.93-1.38	0.202
Ever diabetes	2.27	1.89-2.73	<0.001	1.51	1.23-1.85	<0.001
Follow-up years	1.03	1.02-1.04	<0.001	1.06	1.04-1.07	<0.001
Total therapy						
No therapy	–	–	–	–	–	–
1 drug	1.29	1.10-1.53	0.002	1.10	0.92-1.33	0.061
2 drugs	1.90	1.61-2.24	<0.001	1.39	1.16-1.67	<0.001
3 drugs	2.70	2.23-	<0.001	1.66	1.34-	<0.001

Table 5Univariable and Multivariable Binary Logistic Regression Model to Investigate the Determinants of Normal vs Pathological LV Pattern at Follow-Up	OR	95% CI	*P* Value	Adjusted OR	95% CI	*P* Value
		3.27			2.06	
4 drugs or more	5.23	3.79-7.29	<0.001	2.90	2.02-4.21	<0.001

Abbreviations as in **Table 3**.

Alluvial Plot of the Individual Changes in Left Ventricular Geometry Pattern From Baseline to Follow-Up

The height of each bar is proportional to the number of patients with the corresponding left ventricular geometry pattern, and the width of the ends of each flow line is proportional to the number of patients whose left ventricular geometry pattern changed at follow-up. LVH = left ventricular hypertrophy.

Discussion

Our study aimed to explore sex-related differences in LV geometry patterns in a large cohort of patients with arterial hypertension. We found that LV remodeling was more prevalent in females compared with males at the initial assessment, with a higher occurrence of LVH observed in females, including both eccentric and concentric LVH. The association between sex and LV remodeling persisted throughout the follow-up, indicating that these differences in LV geometry might even increase over time and therefore are not solely attributable to distinct clinical presentations. Prior studies from the Campania Salute Network registry had also noted a higher prevalence of LV hypertrophy in females.**20**,**21** Our study builds on this by establishing a

significant association between female sex and LV remodeling, irrespective of other cardiovascular risk factors like obesity, further emphasizing the role of sex in influencing LV remodeling. The persistent association between female sex and advanced LV remodeling patterns suggests sustained cardiovascular risk for females with arterial hypertension, highlighting the importance of long-term surveillance and tailored interventions to mitigate LV remodeling progression.

Several potential explanations may account for these sex-based differences. Complex social, economic, and structural disparities contribute to differing experiences between females and males.**22** One plausible factor could be the historical oversight of early clinical signs in females, a phenomenon observed in other cardiac conditions such as coronary artery disease and heart failure.**23** This oversight might be linked to factors such as symptom denial and a heightened emphasis on the health of other family members.**23**

Our findings suggest that females experience untreated hypertension for a longer duration than men before accessing health care services, potentially leading to a worse LV geometry pattern due to delayed treatment initiation. However, even after accounting for the duration of hypertension, female sex remained significantly associated with LV remodeling, along with age, diabetes, obesity, and baseline systolic BP. This aligns well with previous observations indicating that progressive BP elevation increases more rapidly in females than in males, starting as early as the third decade of life.**24**

A notable finding in our study is the higher prevalence of eccentric LVH pattern in females compared to males, both at baseline and during follow-up. Traditionally, female sex is linked to concentric remodeling in the general population, while male sex is linked to eccentric LV hypertrophy, likely due to the higher prevalence of coronary artery disease in males.**25-27** By excluding patients with prevalent and incident myocardial infarction, we could partly eliminate this potential confounder.

Furthermore, the response to pathological conditions such as diabetes, obesity, and hypertension differs over time between males and females.**28** Interestingly, while the expression of collagen in human hearts does not differ between sexes, regulators of collagen metabolism vary between sexes. Collagen types I and III are lower in young females than young males, but this ratio reverses with age, with females tending to express higher levels of both types compared to males.**25**,**29** This difference in collagen composition might contribute to varying adaptation to cardiovascular risk factors between sexes.**25**,**29**

Additionally, we observed an increase in the prevalence of concentric hypertrophy mostly in females at follow-up. This may be attributed to visceral adiposity in older females, often associated with systemic inflammation.**30** This inflammatory process can lead to cardiac fibrosis, impairing ventricular distensibility and causing diastolic filling abnormalities, resembling concentric LV hypertrophy.**30**

Study limitation

We recognize inherent limitations in our study due to the observational nature of the Campania Salute Network, which remains susceptible to biases despite extensive multivariable adjustment efforts, also considering that the results hereby reported were not corrected for multiple comparisons and thus the significance threshold of the analysis is to be interpreted with caution. Nonetheless, we have minimized selection and observational biases by enrolling all hypertensive patients and consistently applying a standardized protocol across participants. In addition, although patients were referred by general practitioners and community hospitals, we were unable to stratify the analyses according to the original referring site.

We acknowledge that classification and reclassification of LVH by echocardiography, based on a single assessment, might be challenging because of the intrinsic noise in the measurement. However, echocardiographic assessment of left ventricular mass has previously been

demonstrated to maintain sufficient reliability to be used in clinical practice.**21**,**31**,**32**

Another limitation of our study was that we did not account for death as competing risk. However, we observed only 21 deaths during the follow-up time. Given that we have no information about the cause of deaths for these patients, we decided to exclude these patients from the analysis.

Observational studies like ours cannot establish causal relationships but may generate hypotheses for subsequent mechanistic investigations. Despite this limitation, they are adept at identifying predictors in real-world contexts, aligning with our investigation's primary objective.

Conclusions

The present study highlights significant sex-related differences in LV remodeling patterns among hypertensive patients, underscoring the need for sex-specific approaches in hypertension management and cardiovascular risk reduction strategies.

13. Bromocriptine Treatment and Outcomes in Peripartum Cardiomyopathy

BACKGROUND AND AIMS

Peripartum cardiomyopathy (PPCM) remains a serious threat to maternal health around the world. While bromocriptine, in addition to standard treatment for heart failure, presents a promising pathophysiology-based disease-specific treatment option in PPCM, the evidence regarding its efficacy remains limited. This study aimed to determine whether bromocriptine treatment is associated with improved maternal outcomes in PPCM.

METHODS

PPCM patients from the EORP PPCM registry with available follow-up were included. The main exposure of this exploratory non-randomized analysis was bromocriptine treatment, and the main outcome was a composite endpoint of maternal outcome (death or hospital readmission within the first 6 months after diagnosis, or persistent severe left ventricular dysfunction [left ventricular ejection fraction <35%] at 6-month follow-up). Inverse probability weighting was used to minimize the effects of confounding by indication. Multiple imputation was used to account for missing data.

RESULTS

Among 552 patients with PPCM, 85 were treated with bromocriptine (15%). The primary endpoint was available in 491 patients (89%) and occurred in 18 out of 82 patients treated with bromocriptine in addition to standard of care (22%) and in 136 out of 409 patients treated with standard of care (33%) (p=0.044). In complete case analysis, bromocriptine treatment was associated with reduced adverse maternal outcome (odds ratio [OR] 0.29, 95% confidence interval [CI] 0.10-0.83, p=0.021). This association remained after applying multiple imputation and methods to correct for confounding by indication (inverse probability weighted model on imputed data OR 0.39, 95% CI 0.19-0.81, p=0.011). Thrombo-embolic events were observed in 5.9% of the patients in the bromocriptine group versus 5.6% in the standard of care group (p=0.900).

CONCLUSIONS

Among women with PPCM, bromocriptine treatment in addition to standard of care was associated with better maternal outcomes after 6 months.

14. AI-Guided Screening for Cardiomyopathies in Pregnant and Postpartum Women

Nigeria has the highest reported incidence of peripartum cardiomyopathy worldwide. This open-label, pragmatic clinical trial randomized pregnant and postpartum women to usual care or artificial intelligence (AI)-guided screening to assess its impact on the diagnosis left ventricular systolic dysfunction (LVSD) in the perinatal period. The study intervention included

digital stethoscope recordings with point of-care AI predictions and a 12-lead electrocardiogram with asynchronous AI predictions for LVSD. The primary end point was identification of LVSD during the study period. In the intervention arm, the primary end point was defined as the number of identified participants with LVSD as determined by a positive AI screen, confirmed by echocardiography. In the control arm, this was the number of participants with clinical recognition and documentation of LVSD on echocardiography in keeping with current standard of care. Participants in the intervention arm had a confirmatory echocardiogram at baseline for AI model validation. A total of 1,232 (616 in each arm) participants were randomized and 1,195 participants (587 intervention arm and 608 control arm) completed the baseline visit at 6 hospitals in Nigeria between August 2022 and September 2023 with follow-up through May 2024. Using the AI-enabled digital stethoscope, the primary study end point was met with detection of 24 out of 587 (4.1%) versus 12 out of 608 (2.0%) patients with LVSD (intervention versus control odds ratio 2.12, 95% CI 1.05-4.27; P = 0.032). With the 12-lead AI-electrocardiogram model, the primary end point was detected in 20 out of 587 (3.4%) versus 12 out of 608 (2.0%) patients (odds ratio 1.75, 95% CI 0.85-3.62; P = 0.125). A similar direction of effect was observed in prespecified subgroup analysis. There were no serious adverse events related to study participation. In pregnant and postpartum women, AI-guided screening using a digital stethoscope improved the diagnosis of pregnancy-related cardiomyopathy. ClinicalTrials.gov registration: NCT05438576.

15. How far are we from accurate sex-specific risk prediction of cardiovascular disease? One size may not fit all

This editorial refers to ‘Sex inequalities in cardiovascular risk prediction’, by J. Elliott *et al.*, https://doi.org/10.1093/cvr/cvae123.

Since the term 'risk factor' was proposed for the first time in the Framingham study, multiple cardiovascular risk prediction models over the past decades have been developed to assess an individual's future risk of developing cardiovascular disease (CVD), with the aim to implement certain interventions to those at elevated risk.1 Although sex-specific equations have been adopted in some of the predictive models, in the majority, the same risk variables are used for both males and females (albeit sometimes with different points for a given variable), and the intervention thresholds for males and females are often equal.2–4 Given the known sex differences in risk factors, metabolic physiology, and clinical outcomes associated with CVD, one size may not fit all.

In this issue of the journal, Elliott *et al.*5 used UK Biobank data to evaluate the predictive performance of sparse sex-specific variables for CVD in comparison with the Pooled Cohort Equations (PCE) and QRISK3 CVD risk prediction models, with guideline specific thresholds. Their results showed that the model with sex-specific predictors had similar *C*-statistics in both males and females [i.e. 0.71 (0.70–0.72) for male; 0.72 (0.71–0.73) for female], equivalent or slightly higher than that of PCE [0.67 (0.66–0.68) for male; 0.69 (0.68–0.70) for female] and QRISK3 [0.70 (0.69–0.71) for male; 0.72 (0.71–0.73) for female]. Furthermore, the sensitivity using currently recommended risk thresholds in females was significantly lower than in males, and the use of a lower threshold was associated with increased sensitivity in females.

This study highlights the development of a sex-specific predictive model with the selection of sparse variables, and the attempted use of sex-specific thresholds for more accurate prediction of CVD. Indeed, in addition to the commonly shared risk factors (including hypertension, diabetes, hyperlipidaemia, etc.), there are some female-specific risk factors such as pregnancy and a post-menopausal state, which may accentuate cardiovascular risk. The variation in risk factors for CVD between males and females have been demonstrated in previous studies.6 Female sex itself is an independent risk factor for CVD, and two-thirds of models had been

explicitly developed for males and females separately, although they generally adopted the same factors.1

In the study, Elliott *et al.*5 used sex-specific predictors to develop the predictive model. Nevertheless, the predictive performance with the new model was not significantly improved compared with that of traditional models (all *C*-statistics around 0.7). Indeed, developing new models with improved performance is often challenging with complex designs and the use of additional variables without a marked improvement over older risk models, as shown by Elliott *et al.*5 In contrast, traditional models use some common but important risk factors—these offer the advantage of convenience and ease, whereas complex models with an increased number of variables, especially novel population-specific variables, may make the use of the models less convenient whilst also increasing the assessment cost, finally restricting its applicability. Therefore, an ideal cost-effective predictive model should first be practical especially when used for broad-based screening.

The concept of sex-specific thresholds used for diagnosis and treatment of CVD is still worth exploring. One classic application is the sex-specific thresholds of troponin in patients with suspected acute coronary syndrome (ACS).7 In a study enrolling 48 282 patients suspected ACS, myocardial injury was defined as high-sensitivity cardiac troponin I concentrations > 99th centile of 16 ng/L in females and 34 ng/L in males patients; hence, use of this sex-specific threshold could identify five times more additional females than males with myocardial injury.7 In patients with atrial fibrillation (AF), females were historically at higher ischaemic stroke risk than males, leading to female sex being given an additional point as a risk modifier in the CHA_2DS_2-VASc score for stroke risk stratification.8 Nevertheless, more recent data show overall population stroke rates declining with marginal sex differences in the incidence of AF-related stroke, raising the possibility for female sex to be omitted as a factor when estimating ischaemic stroke risk and the need for oral anticoagulation therapy in patients with AF.8,9

Nevertheless, sex-specific thresholds could provide more accurate diagnostic or preventive value. This is particularly important for the prediction of CVD because inappropriate risk-based management may lead to overtreatment or undertreatment, whereas the development of a sex-specific predictive model with the use of sex-specific thresholds could improve predictive performance. As in the study by Elliott *et al.*5 the sensitivity of the predictive model in females was significantly enhanced when a lower risk threshold was used. Overall, the significantly lower true positive rate for females across all risk models in this study may have potentially skewed the performance, and further validation and assessment of a sparse selection of variables in different populations would be an important task for future studies.

Developing a predictive model with greater accuracy is far beyond using sex-specific formulas and (or) thresholds. In the past decades, great efforts have been made to improve the accuracy of CVD prediction models, particularly through the addition of novel biomarkers such as biochemical measurements, imaging data, and genetic analysis, over and above traditional risk factors. However, the additional practical benefit provided by such markers has been shown to be limited and the cost-effectiveness is questionable, especially in the setting of population-wide screening tests. Also, statistical significance is not the same as clinical significance (and practical application). Risk factors also tend to cluster leading to 'clinically complex' risk phenotypes.10 In more recent years, machine learning has been shown to be a promising tool to improve the predictive performance and risk stratification for CVD, accounting for dynamic changes in risk factors over time.11 The latter is important given that risk is not static but changes with aging and incident comorbidities; however, traditional risk models investigate a risk factor at baseline and record event rates many years later. However, the generalization of machine learning to CVD risk prediction has a long way to go due to the heterogeneity in different population characteristics and the complexity of algorithms in machine learning.

Currently, a universally predictive model applicable to all populations with a high performance is challenging. Derivation and validation of models requires a large number of participants from different regions, races, and socioeconomic backgrounds with abundant variables and continuous longitudinal observation spanning many years, accounting for dynamic changes in risk. This global, highly coordinated and collaborative work is expectedly extremely challenging. On the other hand, even if such a universally predictive model could be developed, this would likely be complex and may not be implemented conveniently as a routine screening tool. Questions remain on the performance of models using a smaller vs. a more exhaustive list of variables, as well as with sex-specific differences in variables included and thresholds used. However, the key sex differences in risk factors, biological and social determinants mean that we have further to go in the quest for a model that accurately and effectively takes that into account.

16. Sex inequalities in cardiovascular risk prediction

1. Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide.1 Risk stratification via accurate prediction of future CVD risk is key to guiding effective early management and prevention, including lifestyle modifications and lipid-lowering therapeutics. A systematic review of CVD prediction models found that the most commonly included variables were age, smoking, systolic blood pressure, history of diabetes, total cholesterol, and high-density lipoprotein cholesterol.2 Alongside ethnicity and history of treated hypertension, these variables are included in the pooled cohort equations (PCEs), which are used in the USA to predict 10-year absolute atherosclerotic CVD risk as a decision aid for recommending lipid-lowering (statin) therapy, with a treatment threshold of 7.5% 10-year absolute risk or greater.3,4 In the UK, QRISK3 is used instead and incorporates additional variables, with a 10% 10-year absolute risk of atherosclerotic CVD used as a

statin treatment threshold.5 However, both the US and UK guidelines note that lower treatment thresholds are likely to be clinically beneficial.6,7 Furthermore, there is evidence for sex- and age-specific treatment thresholds, with worse test sensitivity for younger vs. older adults and women vs. men.8,9

Models including additional variables have been proposed to predict incident coronary artery disease (CAD), with recent examples combining data from electronic healthcare records with polygenic risk scores (PRSs) for CAD10 and blood markers.11 Other recent studies have reported that PRS for CAD/CVD, when considered in isolation, yield a modest or non-significant improvement in predictive performance for CVD risk over traditional risk models.12–16 It has also been suggested that metabolomic data may be predictive of incident CVD, although their clinical utility in risk prediction remains to be established.17–20

Here, we analyse the UK Biobank data set to evaluate sex differences in CVD risk prediction, including use of (i) optimal sex-specific risk predictors and (ii) sex-specific risk thresholds.

2. Methods

2.1 Study participants

The UK Biobank recruited 502 536 volunteers aged 38–73 years between 2006 and 2010. Demographic and lifestyle factors, medical and surgical histories, standardized clinical measurements, and blood samples were collected at baseline. A panel of laboratory tests was performed on stored serum and red blood cells as well as genotyping.21 For the primary analyses, we excluded a total of 198 180 participants: 151 806 with prevalent CVD or missing data for any of the variables included in PCE or QRISK3,14 45 887 on lipid-lowering agents (as PCE and QRISK3 are used to guide the initiation of lipid-lowering therapeutics), and a further 487 who had withdrawn consent, leaving 304 356 participants without prior CVD at baseline for the

present analyses (121 724 men and 182 632 women, *Figure 1*). Among these, a subset of 27 873 men and 40 982 women also had data on nuclear magnetic resonance (NMR) metabolic biomarkers measured in baseline plasma samples. The study complies with the Declaration of Helsinki.

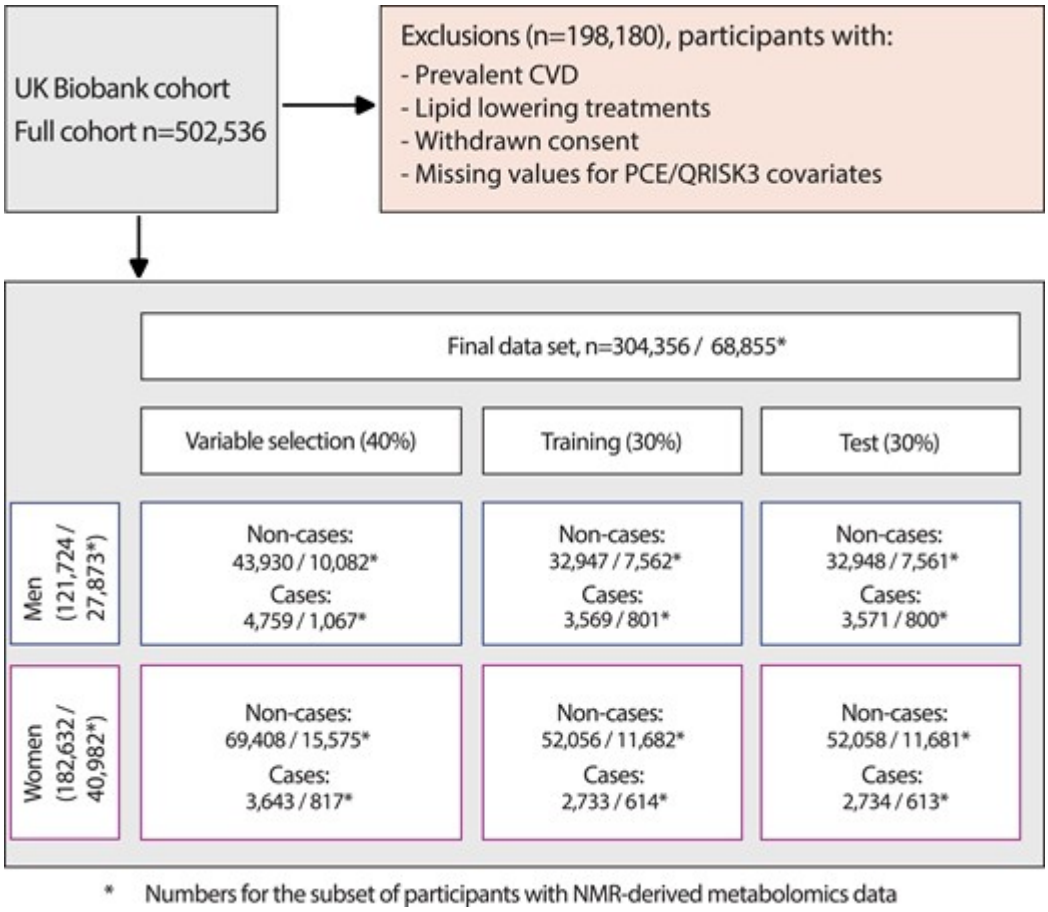

Figure 1

Study design and flowchart. Cases are participants with a CVD event during follow-up including myocardial infarction and its sequelae, angina, non-haemorrhagic stroke, and transient ischaemic attack. Data were randomly split into three sex-stratified, non-overlapping sets: (i) variable selection data set (40%); (ii) training data set (30%), in which Cox models using selected variables were fitted; and (iii) hold-out test data set (30%), in which the predictive accuracy of these models was evaluated and compared with PCEs and QRISK3.

2.2 CVD definition

CVD was defined as myocardial infarction and its sequelae, angina, non-haemorrhagic stroke, and transient ischaemic attack.14 Cases (i.e. people who had a cardiovascular event during follow-up) were identified using linkage to hospital admissions, operation/procedure codes, and death registrations, and prevalent cases were further defined via nurse-administered questionnaire at baseline (see Supplementary material online, *Table S1*). Participants who did not have a recorded cardiovascular event during follow-up are defined here as non-cases, with censoring by availability of hospital admission and mortality data (7 April 2021).

2.3 Study variables

Variables included in PCE3,4 are age, ethnicity (White, Black, and Other), smoking (never, former, and current), diabetes (prevalent self-reported or from hospital records), total and high-density lipoprotein cholesterol, systolic blood pressure (mean of two measurements), and use of antihypertensive medication. QRISK35 includes additional variables: standard deviation of systolic blood pressure, body mass index, family history of CAD, area-level deprivation score (Townsend), medication use including oral steroids and atypical antipsychotics, and self-reported prevalent conditions including chronic kidney disease stages 3–5, atrial fibrillation, migraine, rheumatoid arthritis, systemic lupus erythematosus, severe mental illness, and erectile dysfunction in men. In addition to the above variables, we considered for variable selection 26 further baseline serum biochemistry measurements (excluding oestradiol and rheumatoid factor that were missing in more than 80% of participants)22,23; 23 baseline haematology measurements including full blood count and white blood cell differential24; a PRS for CVD developed using lassosum,25 as previously described14; and NMR-derived metabolic variables (available in ~ 120 000 randomly sampled participants from the whole UK Biobank cohort). The NMR-derived metabolomic profile includes estimated blood levels of (N = 168) annotated molecules including lipoprotein lipids, fatty

acids, and fatty acid compositions, as well as some low-molecular-weight metabolites including amino acids, ketone bodies, and glycolysis metabolites.26

2.4 Statistical analyses

We randomly split the data into three sex-stratified and non-overlapping sets, constraining the ratio of CVD cases to non-cases to be equal in all three data splits (*Figure 1*): (i) a variable selection data set (40%); (ii) a training data set (30%), in which PCE and QRISK3 were calculated/recalibrated (see Supplementary material online, *Methods* and *Figure S1*) and unpenalized Cox models were fit using stably selected variables; and (iii) a hold-out test data set (30%), comparing the predictive accuracy of recalibrated PCE and QRISK3 with the models using stably selected variables. The Cox models used follow-up time as the underlying time variable with CVD event as outcome. In the subset of participants with NMR data, we compared variable selection and model performance excluding and including metabolomic data. After filtering for highly correlated variables and overlap with directly measured blood markers, 18 metabolomic variables were included in our analyses (see Supplementary material online, *Methods* and *Figure S2*) and were available in 68 855 of the 304 356 participants included in our study (*Figure 1*). For biochemical and haematological variables, there was up to 20% missingness with similar proportions for CVD cases and non-cases (see Supplementary material online, *Table S2*). Missing values were imputed using multiple imputation with predictive mean matching over five iterations of chained random forests.27 Skewed variables were log-transformed prior to analyses.

2.4.1 Variable selection

For variable selection, we used LASSO penalized regression in a stability selection framework28,29 to identify reproducible, parsimonious sets of variables that jointly contribute to CVD risk prediction. Briefly, we fit LASSO

Cox models on (N = 1000) 50% independent subsamples of the variable selection data set and estimated, across subsamples, the per-variable selection proportion as a proxy for the variable importance. Model calibration was achieved by jointly identifying (i) the penalty parameter λ (controlling the sparsity of the LASSO model) and (ii) the threshold in selection proportion π (controlling the stability of the model, conditional on the penalty) above which a feature was considered as stably selected. These parameters were obtained by maximizing a likelihood-based stability score using the *sharp* package in R.29 We also performed sensitivity analyses assessing the reliability of the LASSO stability selection, using 100 subsampled variable selection data sets (see Supplementary material online, *Methods*).

2.4.2 Predictive performance

We calculated predictive accuracy (*C*-statistics) as well as sensitivity and specificity at relevant risk thresholds for 10-year risk (7.5% threshold for PCE, 10% threshold for QRISK3, and both 7.5 and 10% thresholds for models using stably selected variables). We used logistic regression models to perform receiver operating characteristic (ROC) analyses, reporting the mean and 95% confidence intervals of the area under the ROC curve (AUC). We also used a nested approach where log hazards from PCE and QRISK3, respectively, were forced into the LASSO stability selection models in place of their constituent variables. In addition, we calculated sensitivity and specificity at 5% 10-year risk threshold in women across all models.

Statistical analyses were performed using R version 4.2.2.30

3. Results

Mean age at baseline in men was 54.4 years in non-cases and 58.9 years in cases and 55.2 and 60.0 years, respectively, in women. A total of 11 899 men and 9110 women were diagnosed with CVD during the period of follow-up (median 12.1 years). Descriptive statistics, stratified by sex and case

status, are shown in Supplementary material online, *Table S3*. Corresponding descriptive statistics for the subset with metabolomic data are reported in Supplementary material online, *Table S4*.

Our stability selection model consistently selected 12 variables in both men and women (*Figure 2*): age, albumin, antihypertensive medication, apolipoprotein B, atrial fibrillation, C-reactive protein, current smoker, cystatin C, family history of CAD, glycated haemoglobin, systolic blood pressure, and a PRS for CVD. In addition, apolipoprotein A1, lipoprotein(a), white blood cell count, and deprivation index were selected in men only and triglycerides in women only (see Supplementary material online, *Table S5*). Including variables beyond those stably selected did not substantially improve model performance (see Supplementary material online, *Figure S3*).

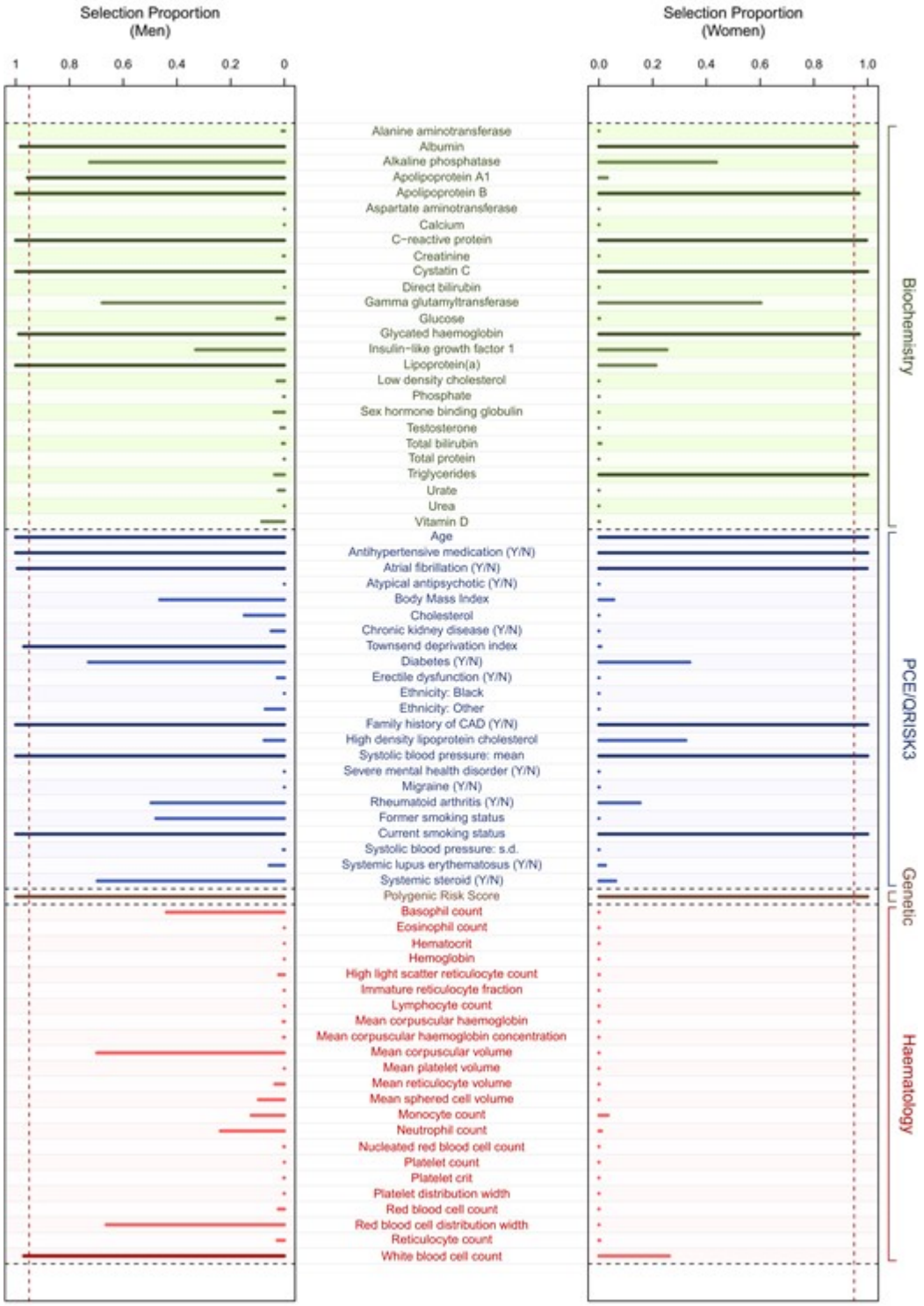

Figure 2

Stability selection LASSO. Selection proportions from LASSO stability selection calculated from (*N* = 1000) subsamples in (*N* = 48 689) men (*left panel*) and (*N* = 73 051) women (*right panel*). Explanatory variables considered include those contributing to PCE and QRISK3 scores (blue),

genetic (brown), biochemical (green), and haematological (red) variables. Darker colours indicate stably selected variables (16 and 13 in men and women, respectively) as defined by variables with selection proportion above the calibrated threshold in selection proportion (vertical dark red dashed line).

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ROC analyses with logistic models for incident CVD in test data showed improvement in predictive accuracy when using stably selected variables vs. recalibrated PCE but not for QRISK3: in men, AUCs were 0.67 (0.66–0.68) for PCE and 0.70 (0.69–0.71) for QRISK3 vs. 0.71 (0.70–0.72) for models using stably selected variables; in women, they were 0.69 (0.68–0.70) for PCE and 0.72 (0.71–0.73) for QRISK3 vs. 0.72 (0.71–0.73) for stably selected variables (*Figure 3*).

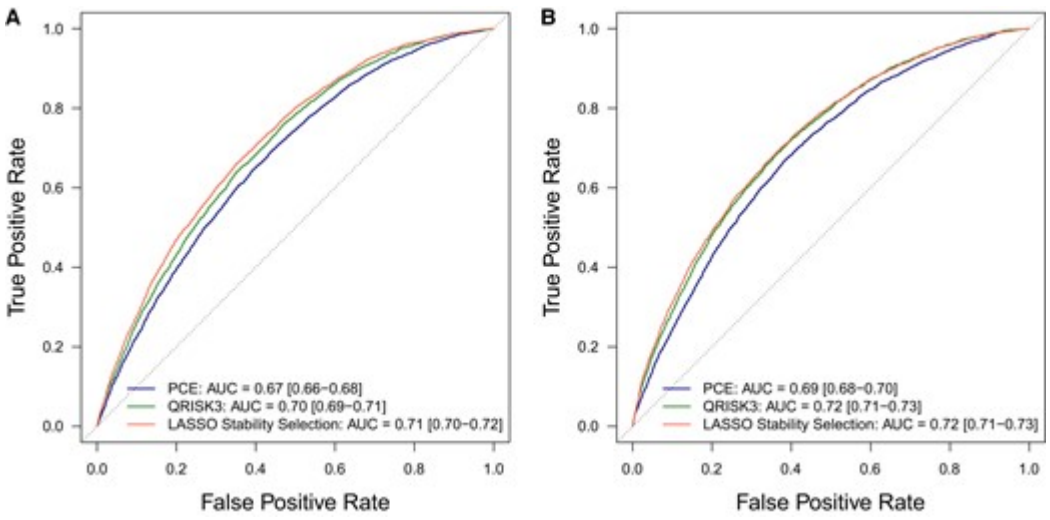

Figure 3

CVD prediction in test data. ROC curves for logistic models predicting 10-year incident CVD in (*N* = 36 519) men (*A*) and (*N* = 54 792) women (*B*) in test data, where models use either recalibrated PCE (blue line), recalibrated QRISK3 (green line), or sex-specific stably selected variables (red line) in test data. We report the mean and 95% confidence intervals for the AUC.

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Table 1 shows 10-year risk prediction reclassification, sensitivity, and specificity for LASSO stability selection variables vs. PCE (7.5% risk threshold) and QRISK3 (10% risk threshold). Test sensitivity was markedly lower in women than men for all models: at 7.5% 10-year risk, sensitivity was 65.1 and 68.2% in men and 24.0 and 33.4% in women for PCE and models using stably selected variables, respectively; at 10% 10-year risk, sensitivity was 53.7 and 52.3% in men and 16.8 and 20.2% in women for QRISK3 and stably selected variables, respectively. Specificity was correspondingly higher in women than men. However, the sensitivity in women at 5% 10-year risk threshold increased to 50.1, 58.5, and 55.7% for PCE, QRISK3, and stably selected variables, respectively (*Table 2*).

Reclassification of CVD cases and non-cases in test data comparing Cox survival models using LASSO stability–selected variables with validated risk prediction algorithms: (A) at 7.5% 10-year risk threshold for PCE and (B) at 10% 10-year risk threshold for QRISK3; sensitivity and specificity are shown at the relevant risk thresholds

A PCE vs. LASSO				
Men				
PCE Predicted 10-year risk (%)		**LASSO stability selection**		
		Predicted 10-year risk (%)		**Reclassified (%)**
		<7.5	**≥7.5**	
Cases	<7.5	808	439	35.2
	≥7.5	329	1995	14.2

A PCE vs. LASSO					
Men					
PCE Predicted 10-year risk (%)		**LASSO stability selection**			
		Predicted 10-year risk (%)		**Reclassified (%)**	
		<7.5	**≥7.5**		
Non-cases	<7.5	16886	2851	14.4	
	≥7.5	3610	9601	27.3	
				LASSO%	**PCE%**
Sensitivity (at 7.5% 10-year risk)				68.2	65.1
Specificity (at 7.5% 10-year risk)				62.2	59.9
Women					
PCE Predicted 10-year risk (%)		**LASSO stability selection**			
		Predicted 10-year risk (%)		**Reclassified (%)**	
		<7.5	**≥7.5**		
Cases	<7.5	1631	448	21.5	

Women				
PCE Predicted 10-year risk (%)		**LASSO stability selection**		
		Predicted 10-year risk (%)		**Reclassified (%)**
		<7.5	**≥7.5**	
	≥7.5	189	466	28.9
Non-cases	<7.5	43 785	3149	6.7
	≥7.5	2430	2694	47.4
			LASSO%	**PCE%**
Sensitivity (at 7.5% 10-year risk)			33.4	24.0
Specificity (at 7.5% 10-year risk)			88.8	90.2
B QRISK3 vs. LASSO				
Men				
QRISK3 Predicted 10-year risk (%)		**LASSO stability selection**		
		Predicted 10-year risk (%)		**Reclassified (%)**
		<10	**≥10**	

B QRISK3 vs. LASSO				
Men				
QRISK3 Predicted 10-year risk (%)		**LASSO stability selection**		
		Predicted 10-year risk (%)		**Reclassified (%)**
		<10	**≥10**	
Cases	<10	1391	264	16.0
	≥10	312	1604	16.3
Non-cases	<10	22 431	1499	6.3
	≥10	2483	6535	27.5
			LASSO%	**QRISK3%**
Sensitivity (at 10% 10-year risk)			52.3	53.7
Specificity (at 10% 10-year risk)			75.6	72.6
Women				
QRISK3 Predicted 10-year risk (%)		**LASSO stability selection**		
		Predicted 10-year risk (%)		**Reclassified (%)**

		<10	≥10	
Cases	<10	2058	218	9.6
	≥10	124	334	27.1
Non-cases	<10	48 269	1358	2.7
	≥10	984	1447	40.5

	LASSO%	QRISK3%
Sensitivity (at 10% 10-year risk)	20.2	16.8
Specificity (at 10% 10-year risk)	94.6	95.3

Reclassification of CVD cases and non-cases in test data among women using 5% 10-year risk thresholds: (A) recalibrated PCEs and (B) QRISK3 compared with Cox survival models using LASSO stability selected variables; (C) shows sensitivity and specificity for each model at 5% 10-year risk threshold

A PCE vs. LASSO	
PCE Predicted	**LASSO stability selection**

		Predicted 10-year risk (%)		Reclassified (%)
		<5	≥5	
Cases	<5	962	402	29.5
	≥5	249	1121	18.2
Non-cases	<5	34 755	4306	11.0
	≥5	4439	8558	34.2
B QRISK3 vs. LASSO				
QRISK3 Predicted 10-year risk (%)		**LASSO stability selection**		
		Predicted 10-year risk (%)		**Reclassified (%)**
		<5	**≥5**	
Cases	<5	959	175	15.4
	≥5	252	1348	15.8
Non-cases	<5	35 380	2285	6.1
	≥5	3814	10 579	26.5
C Sensitivity and specificity at 5% 10-year risk threshold				

	LASSO%	QRISK3%	PCE%
Sensitivity (at 5% 10-year risk)	55.7	58.5	50.1
Specificity (at 5% 10-year risk)	75.3	72.4	75.0

In sensitivity analyses where PCE or QRISK3 log hazards were included in lieu of the constituent variables, stably selected variables differed slightly from the main analyses (see Supplementary material online, *Figure S4*). This did not affect model performances, with similar *C*-statistics, sensitivity, and specificity (see Supplementary material online, *Table S6*).

Among the subset of (*N* = 68 855) participants with available metabolomic data, glycoprotein acetyls was selected in women only, in preference to C-reactive protein (see Supplementary material online, *Figure S5*), with no improvement in predictive performance (see Supplementary material online, *Figures S6* and *S7*). Assessment of the reliability of LASSO stability selection showed similar variable sets across 100 subsampled iterations (see Supplementary material online, *Methods* and *Figure S8*).

4. Discussion

In this large population-based cohort, use of sex-specific stably selected variables improved predictive performance for CVD beyond PCE but not QRISK3, although QRISK3 was also developed selecting from an extensive set of risk predictors.5 Among the variables selected in both men and women, some are already included in PCE and QRISK3, while others used in these risk calculators were not selected (diabetes status, ethnicity, high-density lipoprotein, and total cholesterol). At the current clinical risk thresholds, sensitivity was much lower in women (with higher specificity)

than in men for both PCE and QRISK3. A higher proportion of incident CVD cases might therefore go untreated in women than men using a common risk threshold for both sexes, as is current practice.

Our results concerning test sensitivity by sex are consistent with previous findings for PCE. In an analysis of PCE among 3685 participants in the Framingham Offspring Study, sensitivity was lower in women than men at the clinically used 7.5% 10-year risk threshold, except at the oldest ages; the authors suggest using a 5% risk threshold at younger ages (40–55 years).8 In 1685 patients of the YOUNG-MI registry, who had a myocardial infarction aged 50 years or below, sensitivity of PCE in women was around half that in men at the 7.5% risk threshold. However, sensitivity in women at the 5% risk threshold was similar to that in men at the 7.5% threshold.9 Together with our own findings, these results suggest that sex-specific risk thresholds should be considered for clinical implementation to avoid sex inequality in CVD risk prediction.

Sex-specific differences in CVD risk prediction are not well understood. They may reflect underlying physiological differences, including the impact of sex hormones, vascular remodelling, lipid metabolism, and endothelial function.31,32 In our study, among lipids, triglycerides33 were selected in women only and lipoprotein(a)34,35 and apolipoprotein A136–38 in men only. Apolipoprotein B was selected in both men and women, replacing more standard lipid measures currently included in PCE and QRISK3, consistent with it being a better risk predictor of incident CVD.39,40 In keeping with this, both the European Society of Cardiology41 and the 2019 American College of Cardiology/American Heart Association guidelines on primary prevention of CVD42 have highlighted the utility of apolipoprotein B to improve risk stratification.

Systemic inflammation is an important component of CVD risk, and some of the selected variables reflect this: while white blood cell count was selected in men only, serum albumin,43 C-reactive protein44 (acute phase reactants), and cystatin C (a sensitive marker of renal function45,46) were selected in

both men and women. Among NMR metabolomic variables, glycoprotein acetyls47–49 were selected in women only in preference to C-reactive protein, but this did not improve predictive accuracy. In addition, glycated haemoglobin, a biomarker used in the diagnosis and monitoring of diabetes and non-diabetic hyperglycaemia50 (both pro-inflammatory states),51 was stably selected in preference to diabetes status in both men and women, in keeping with it being a continuous and therefore more informative variable. Given that glycated haemoglobin is increasingly recorded in electronic health records and offers a superior predictor of CVD risk, a strong case can be made for its inclusion in CVD risk calculators.

Use of PRS in CVD risk prediction remains controversial14,52; here, it was stably selected in both men and women but made only modest contribution to predictive accuracy, in keeping with previous analyses of UK Biobank and other data.14,15 Family history of CAD, which may reflect common lifestyle and socio-economic factors as well as genetic risk,34 was also stably selected alongside PRS, indicating that they both jointly and independently contribute to CVD risk.

4.1 Limitations

We only included participants aged 38–73 years at baseline who were mostly of European ancestry; the participants were on average healthier, were less deprived, and have lower mortality than the general population and therefore may not be fully representative.53 While PCE was developed in US cohorts, the present study uses a UK-based cohort; we performed model recalibration to correct for population differences54 and included the standard risk prediction tool (QRISK3) used in the UK. Other potentially important predictors including coronary artery calcium were not measured, and their inclusion may further improve risk prediction or potentially compete with variables selected in our models.55 The UK Biobank does not have complete prescription data during follow-up, so it is likely that some participants' CVD risk would have been modified from baseline through clinical management. Cost–benefit and decision analyses would be needed

before implementing either sex-specific risk thresholds or an enhanced predictive score. Variable selection, training, and test data were drawn from the same population; external validation in different cohorts and settings would help to generalize our findings to other populations.

4.2. Conclusions

Use of sparse sex-specific variables improved CVD risk prediction compared with PCE but not QRISK3. At current risk thresholds, PCE and QRISK3 work less well for women than men, but sensitivity was improved in women using a 5% 10-year risk threshold. Use of sex-specific risk thresholds should be considered in any re-evaluation of CVD risk calculators.

17. Sex and gender specific pitfalls and challenges in cardiac rehabilitation: a working hypothesis towards better inclusivity in cardiac rehabilitation programmes

Introduction

Cardiac rehabilitation (CR) is defined as an interdisciplinary comprehensive programme based on physical training, with a concomitant complementary counselling made by trained physiotherapists, changes in modifiable cardiovascular (CV) risk factors, psychosocial support, and patient education about nutritional assessment.1,2 CR represents a pivotal tool in improving exercise capacity, quality of life, and clinical outcomes in different CV diseases (CVD), through different mechanisms (*Figure 1*). Following evidence from epidemiology and clinical studies, the most recent European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend CR in patients with several CVD, enlisted in *Table 1*; in brief, CR is recommended by guidelines in coronary artery disease in order to reduce CV mortality and rehospitalisations,3–5 in patients affected by acute myocardial infarction (MI), coronary artery bypass grafting (CABG), percutaneous coronary

intervention (PCI), pulmonary arterial hypertension,6,7 and in chronic heart failure (HF) to improve exercise capacity and quality of life and reduce HF hospitalisation.8,9 In addition, despite the lack of a specific guideline-based recommendation, a recent position paper made by Ambrosetti *et al.*10 suggests CR also for valve surgery, both for minimally invasive cardiothoracic surgery and aortic valve replacement, to improve short-term physical activity.

Figure 1

Wide beneficial effects of exercise training and cardiac rehabilitation in patients with heart failure.

Table 1

European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) recommendations for cardiac rehabilitation in cardiovascular diseases

	ESC guidelines	**ACC/AHA guidelines**	**Notes**
Heart failure	IA (2021)	IA (2022)	
Acute coronary syndromes			
Persistent ST-segment elevation	IA (2023)	IB*(2014)	*Either Before Hospital discharge or during first outpatient visit
Unstable angina	IA (2023)	IB* (2014)	°Exercise-based cardiac rehabilitation/secondary prevention programmes are recommended for patients with STEMI (Level of Evidence: B)
Patients with ST-segment elevation	IA (2023)	IB° (2013)	
Chronic coronary syndromes	IA (2019)	I§ (2023)	§All patients with chronic coronary disease and appropriate indications should be referred to a cardiac rehabilitation programme to improve outcomes. Level of

	ESC guidelines	ACC/AHA guidelines	Notes
			evidence (LOE) A: After recent MI, percutaneous coronary intervention, or CABG; LOE B-R: With stable angina or after heart transplant; LOE C-LD: after recent spontaneous coronary artery dissection event
Myocardial revascularization:			
Coronary artery bypass graft surgery (CABG)	IA (2018)	IA§ (2021)	§Either before hospital discharge or during first outpatient visit
Percutaneous coronary intervention	IA (2018)	IA§ (2021)	
Aortic disease		IC£ (2022)	£For patients who have undergone surgery for aortic aneurysm or dissection, post-operative cardiac rehabilitation is recommended
Peripheral	IA (2017)^	IA (2016)	^For supervised exercise

	ESC guidelines	ACC/AHA guidelines	Notes
arterial disease			training in patients with intermittent claudication. I C for unsupervised exercise training when supervised exercise training is not feasible or available. IIa C when daily life activities are compromised despite exercise therapy, revascularization should be considered. IIa B when daily life activities are severely compromised, revascularization should be considered in association with exercise therapy
Pulmonary hypertension	IA (2022)"		"Supervised exercise training is recommended in class IA for patients with PAH under medical therapy

Nevertheless, CR is still globally largely under prescribed. For instance, among 366 103 eligible Medicare beneficiaries in 2016, it has been reported that only 89 327 (~ 24%) attended CR, of which ~ 57% completed more than

24 CR sessions and around 27% completed 36 CR sessions, implicating missed opportunities to potentially improve health outcomes.11

As reported in the most recent position paper of the Italian Association for Cardiovascular Prevention and Rehabilitation (formerly GICR-IACPR),12 based on the findings of a multi-centre survey,13 the total offer remains still very low, involving no more than 30–35% of the potential patients despite an increase in a 5-year period of around 20% of the number of facilities addressing CR.

In this context, the lack of accessibility to CR programme with clear sex-based disparities is a matter of immediate concern14; women are less likely to be enrolled and complete CR compared with men.11,15,16 In addition, the lower attendance of women to CR programme has been reported to be dependent on a gendered cluster of vulnerability which include specific socio-economic, psychological, and cultural patterns. Indeed, gender is a complex socio-cultural construct characterized by four domains (gender identity, relation, role, and institutionalized gender). Beyond biological sex, sociocultural gender represents a major driver of the disparities in the access to CR programme.17

Therefore, the aim of the present review is to shed light upon sex and gender differences in CR, their underlying causes, their effects on clinical outcomes, and the possible strategies to improve this trend.

Cardiovascular rehabilitation programmes: why sex and gender matter

In recent years, there has been an increasing awareness on how ‘sex’ and ‘gender’ capture different aspects of people and constantly intersect to shape health and diseases.18 While sex identifies the biological attributes (that are dependent on chromosomes, genes, reproductive, and endocrine systems), ‘gender’ is a multi-dimensional concept that comes from social science that can be broken down in four main domains: (i) gender identity, that is the personal perception of one's own gender (which might be different from the sex a person is assigned at birth), (ii) gender roles, which include behaviours

and attitudes considered appropriate by the society on basis of the sex, (iii) gender relations, that consist on how one interacts with others and how is treated according to the sex and gender, and (iv) institutionalized gender, that mirrors the structural distribution of power between genders in the political, educational, religious, medical, cultural, and social institutions of a society18,19—see *Figure 2*. Sex and gender might be difficult to tease apart and frequently they are interconnected. The main goal of sex and gender informed medicine is to deliver fair and equitable, patient-specific treatments to improve and strengthen both therapy and patients' prognosis. In the CV clinical setting, the awareness on the impact of sex and gender as modifiers of patient outcomes has increased overtime and recently guidelines have been provided on how to integrate sex and gender in CV research.20 Furthermore, reporting of SOGIE (sexual orientation and gender identity and expression) data have been strongly recommended to guarantee equity, inclusion, and diversity in evidence that guide CV clinical work.21

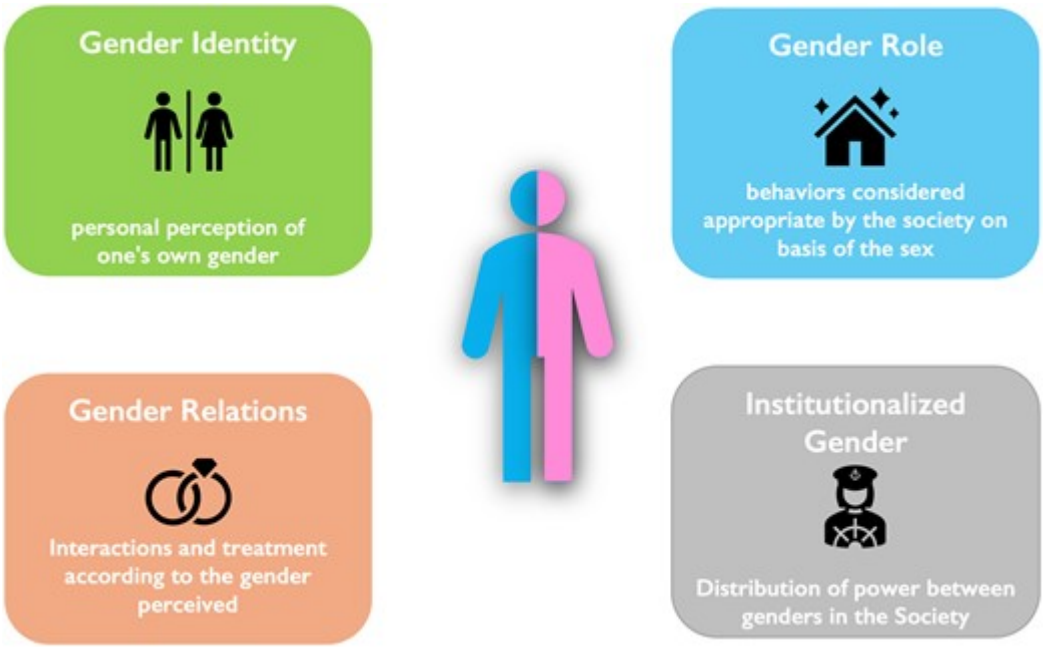

Figure 2

Description of the four domains that characterize the definition of gender.

In the context of CR, it has been demonstrated that there are remarkable sex disparities in CR referral, participation, and completion.22

Generally speaking, there is a lack of facilities dedicated to CR represented by only one spot for every seven patients in need, with a great need for developing countries.23 To date, it is not understood how much gender, broadly viewed as a set of the four constituent domains, influences reduced therapeutic adherence to CR. Therefore, in the absence of evidence, it is appropriate to parcel out its domains to postulate its importance. The difference in CR referral and participation among sexes is consistent with several evidence showing key distinction in clinical presentation, diagnosis, treatment, and clinical outcomes of CV patients.22 In a recent review Arcopinto *et al.*19 highlighted the involvement of sex-specific factors, such as role of oestrogens and pregnancy-related cardiomyopathies, in the incidence of different HF patterns, with women affected more frequently by HF with preserved ejection fraction and higher number of comorbidities. Instead, male individuals showed a predisposition of developing HF with reduced ejection fraction (HFrEF), due to a higher incidence of coronary artery disease and MI. In this regard, the large under-representation of women in clinical trials leads to an incomplete characterisation, and thus knowledge, of a large group of patients. This clinical scenario is further tangled by the presence of gendered socioeconomic and cultural differences between men and women that transcend the mere biological sex.

Specifically, lower rates of women in comparison with men (18.9% vs. 28.6%) have been reported in CR participation, with a decrease as age increases.11 Due to the greater burden of CV risk factors and the higher mortality rate,24 it has been suggested that theoretically women would benefit the most from secondary prevention through CR; yet, they are still less likely to receive a proper CR referral, with a significant impact on their health status. With this regard, among 48 993 patients of the American Heart Association Get with The Guidelines Coronary Artery Disease registry, Li *et al.*15 found that women were 12% less likely to be referred to CR than men, even though the CR referral was associated with a reduction of 40% in 3-years all-cause mortality, and women with a CR referral at hospital discharge showed a lower mortality when compared with those who did not.

It is not known whether the reduced participation in CR depended on a lack of physician referral or whether, after the CR prescription, patients decided not to participate. Despite a slight increase in CR referral rate overtime, this positive trend involved men more than women as depicted in a study among Medicare beneficiaries with HFrEF from the 2014 to 2016.16 In fact, among 11 696 hospitalized HF patients, only 4.3% participated in CR within 6 months of HF hospitalisation, with lower participation in women vs. men (3.3% vs. 5%; $P < 0.001$). The same picture was obtained for outpatients with HF: among 11 832 patients with outpatient encounters for primary HF diagnosis without a hospitalization event, only 2.2% participated in CR within 6 months of the outpatient encounter.16 Samayoa *et al.*25 showed that <40% of women with acute coronary syndrome (i.e. MI or unstable angina), chronic stable angina, stable chronic HF, or undergoing PCI, CABG surgery, cardiac valve surgery, cardiac transplantation, or cardiac resynchronization therapy eligible for CR were enrolled, highlighting a 36% lower enrolment rate in women compared with men. In a meta-analysis, Colella *et al.*26 showed that CR referral rates for women were 39.6% on average compared to 49.4% for men. Colbert *et al.*27 in a recent study demonstrated that, in a cohort of 25 958 patients with coronary artery disease, 6374 were women and there was a lower rate for females than males of CR referral (31.1% vs. 42.2%) and completion (50.1% vs. 60.4%). The survival was greater among patients who attended CR compared to those who were referred but did not participate; moreover, women not referred to CR exhibited the highest mortality of all subjects and a higher mortality when compared with men not referred.27 In fact, women referred to CR, even if they did not attend, showed a significantly improved survival when compared to those not referred and even more whether they completed the programme; likewise, men exhibited survival benefits derived from referral and even more so from participation in CR. However, the relative survival benefit derived from the completion of CR was larger in women than in men.27 Therefore, the benefits from CR are known among women, but difficulties related to transportation and family responsibilities often may affect their participation in CR programme. A recent retrospective study

from the United States on patients enrolled in intensive-cardiac-rehabilitation (ICR) from January 2016 to December 2020 stressed the importance of not exercise-related components of CR in order to reduce the barriers in participation and the gap between sexes.28 Among 15 613 patients the rates of participation in ICR were about 44% for women (*n* = 6788) and 56% for men (*n* = 8825), demonstrating a lower women-disparity than in previous studies.28 Furthermore, the difference in ICR completion was lessened with an exhibited rate of 63.3% for women and 65.9% for men.28 The adherence to CR shows sex differences: men and women enrolled in CR adhered to 68.6% and 64.2% of prescribed sessions, respectively29 (*Table 2*).

Main studies highlighting the under-representation of women in cardiovascular rehabilitation programmes

Study	**Main results**
Ritchey MD, 2020.11 Observational study. 366.103 CR-eligible beneficiaries	89 327 (24.4%) participated in CR, of whom 24.3% initiated within 21 days of event and 26.9% completed CR. Participation: women (18.9%) vs. men (28.6%)
Samayoa L, 2014.25 Systematic review and meta-analysis of 26 eligible observational	45.0% of men and 38.5% of women enrolled in CR. Women 36% less likely to be enrolled in a rehabilitation

Study	Main results
studies. 297 719 participants (128 499 [43.2%] women)	programme
Colella TJ, 2015.26 Meta-analysis of 19 observational studies. 241 613 participants (80 505 [33.3%] women)	In the pooled analysis (39.6%) significantly less likely to be referred to CR compared to men (49.4%)
Colbert JD, 2015.27 Retrospective cohort study. 25 958 subjects (6374 [24.6%] women) with at least one vessel CAD.	Among females reduced rates of CR referral (31.1% vs. 42.2%) and completion (50.1% vs. 60.4%). Women completing CR experienced the greatest reduction in mortality with a relative benefit greater than men.
Hussain Jafri SH, 2023.28 Retrospective cohort study. 15 613 patients (6788	ICR completion rates were 64.7% overall and nearly equal between men and

Study	Main results
[44%] women) enrolled in 46 Ornish-intensive cardiac rehabilitation (ICR) programmes	women (63.3% women vs. 65.9% men)
Oosenbrug E, 2016.29 Meta-analysis including 14 studies. 8176 participants (2234 [27.3%] women).	Cr adherence ranged from 36.7% to 84.6% of sessions, with a mean 66.5 ± 18.2% (median, 72.5%). Men and women enrolled in CR adhered to 68.6% and 64.2% prescribed sessions, respectively.
Ghisi GLM, 2023.30 Cross-sectional study. 2163 patients (916 [42.8%] women) from 16 countries across all 6 WHO regions.	1239/57.8%) patients referred to CR. Differences in referral rate to CR according to sex: 368 women (40.4% of the female group) vs. 866 men (71.0% of the male group). 571 (27.8%) patients participated in CR. Differences in participation rate in CR according to sex:

Study	Main results
	284 women (34.1% of the female group) vs. 283 men (23.5% of the male group).

Gender issues in cardiac rehabilitation

The drivers of the abovementioned sex disparities in CR utilization might be influenced by the socio-economic, psychological, and cultural differences, which are part of the 'gender' concept.31,32 Specifically, barriers for accessing CR have been reported to be strongly dependent by both individual and structural levels.2 Although there are still no specific studies directed towards understanding the impact of various gender domains on CR, the application of a gender-based framework to understand obstacles and challenges of CR among patients eligible for it can be very informative.

Gender identity and sexual orientation

Among the concept of gender identity, a vast spectrum of self-perception exists (girls, women, boys, men, and gender diverse people). With the term 'transgender' it is defined a person who does not identify with the sex assigned at the birth in contrast to 'cisgender', in which sex and gender match. According to the minority stress theory, the transgenders represent a minority of population characterized by disparities in the access to healthcare system, due to social barriers, namely gender non-affirmation (e.g. being called by incorrect pronoun or name), stigma, discrimination, rejection, hypervigilance, concealment, and victimization that influence negatively their mental and physical health.33 In the report of the 2015 U.S. transgender survey34 came to light numerous difficulties for transgender people in terms of adequate access to health care due to economic up to social aspects. In fact, the insurance coverage was often denied due to being transgender or because of care related to gender transition. A higher rate of

poverty and unemployment was frequent among this population and one-third of them showed in the previous year at least a negative experience related to the gender identity in terms of verbal harassment or treatment refused. 23% of them rejected to see a doctor due to the fear of mistreatment for being transgender. Moreover, a great number of transgender people wanted counselling at certain point of the life, and discrimination and marginalization contribute to the psychological distress that could result in a high rate of suicide attempts. Alzahrani *et al.*35 depicted that men who are transgender had a significant higher prevalence of MI compared to cisgender women and cisgender men; conversely women who are transgender showed a significant higher prevalence of MI compared with cisgender women but not when compared with cisgender men.35 In a recent review Connelly *et al.*36 collected some retrospective studies carried on adult transgenders to investigate the CV effects of hormonal therapy. The authors underlined that, in contrast with current evidence, there were discrepant results regarding the relationship between the use of oestrogens by transgender females (TGFs) that are individuals assigned to male sex who identify themselves as female, and an increased risk of MI and ischaemic stroke. Furthermore, studies on transgenders are limited and contradictory and often it remains unclear if CV morbidity and mortality are only ascribable to the hormonal therapy or if there is a component related to the natal sex. In addition, the results are subordinated to the rate of traditional CV risk factors, unhealthy behaviours and additional risk factors (i.e. HIV infection) in this population.

Gender roles

For female caregivers, familial and household responsibilities represent an influential obstacle to CR.31 More frequently women put forward familial responsibilities as obstacles for CR, having difficulties to make time for their prevention. Moreover, sometimes, women consider exercise training as an inappropriate behaviour for a lady.37,38 Additionally, because of logistic problems such as dependence on others for transportation and, differently from men, less encouragement from the spouse, women's attendance at CR decreases.37 To this extent, it would be appropriate for health care

authorities to be made aware and alerted to these disparities so that appropriate corrective measures may be placed.

Gender relations

In a meta-analysis, it has been demonstrated that being married/partnered is associated with a significant higher attendance at CR in patients with coronary heart disease.39 Among these patients, those married or with a partner were 1.5–2 times more likely to attend at outpatient CR. Among patients referred to CR after acute MI the baseline characteristics of non-participants compared with participants were more likely to be elderly, female, and with more CV risk factors and comorbidities.40–42 One hypothetical intervention that could be implemented would be to provide psychotherapeutic-relational support, especially for those individuals whose CV risk is remarkably high.

Institutionalized gender

Unemployed and less educated people and those with lower income had a lower participation.41 In the literature, there are several qualitative studies on women's barriers to CR and on sex differences in relation to these obstacles, but only few quantitative studies. Three quantitative studies on sex differences in CR barriers used a validated scale, the cardiac rehabilitation barrier scale (CRBS).43 One of them, carried on patients of a high-income and very gender-equal Canadian country, showed no sex differences in total number of CR barriers, but a diverse nature of barriers according to sex.44 Conversely, another study, conducted on patients of middle-income and gender-unequal Iranian country, exhibited significantly greater overall barriers among women and in addition to the sex differences of the former study showed some differences related to the socioeconomic status (i.e. cost, transportation, and distance).45 Ghisi *et al.*30 in a landmark cross-sectional study carried on 2163 patients, of which 916 were women (42.8%), from 16 countries across six WHO regions from October 2021 to March 2023, had shown that women's barriers to CR were greatest

in the Western Pacific and South East Asian regions and, in both cases, had individuated the lack of CR awareness as major responsible. The CRBS was used to assess the barriers perceived by patients to CR enrolment and adherence.30 Furthermore, women's unemployment increased barriers to CR. On one hand, among non-enrolled referred women, obstacles were lack of awareness of CR, absence of contact by the programme, cost, and the belief that exercise would be tiring or painful. On the other hand, enrolled women identified as greatest barriers to adherence the distance, transportation, and family responsibilities.30

Summarizing, some of the most frequent issues reported by patients in relation to reduced CR attendance are anxiety to exercise, overburden due to medical appointments, barriers in the interaction with CR staff, lack of awareness or skepticism about the resulting benefits, logistical problems due to distance from the hospital, costs, transportation/parking, employment, and social and familial responsibilities31,46 (*Figure 3*). The lack of CR referral and the hesitation of women due to emotional, relational, economic, cultural, and logistical barriers contribute to a lower level of participation or adherence to CR.46,47 Several studies had examined the principal barriers that women mentioned for non-attendance at CR. Some of these are related to personal issues (e.g. insufficient time, lack of motivation, religious conflicts, economic, and logistical difficulties), whereas others are associated with interpersonal aspects, linked to inadequacy in social and familial support—which correlates with the domain of gender relations and employment—correlated with the domain of institutionalized gender.48 In a secondary meta-synthesis, Angus *et al.*37 observed that gender issues and socioeconomic status are involved in sex disparities when accessing rehabilitation. More precisely, on the one hand difficulties related to employment duties and transportation, especially if there is a lack of financial resources, are more frequently mentioned by men as a cause of non-attendance. On the other hand, women advocate more frequently domestic, familial, and economic responsibilities; in addition, even in the case of no enrolment fees, women have to make time for their prevention,

paying for a housekeeper or family caregiver.37 In a recent systematic review, Galati *et al.*49 underlined that women who do not complete the CR programme were significantly younger, affected by more risk factors, and with greater rate of anxiety and depression in comparison with women who complete CR. Lastly, physicians play a crucial role in addressing candidate patients to rehabilitation, yet often they are perceived as barriers to referral.50

Figure 3

Some of the gender issues on the attendance at cardiac rehabilitation. Access to CR can become cumbersome in the presence of several superposed gender-related issues which result in a burden too great to be carried, ultimately leading to drop out of this secondary prevention.

How to assess the gender?

The lack of a standardized measure of gender might be an obstacle for the integration of sex and gender in research and clinical practice. Several operational frameworks for integrating gender in clinical studies have been published.20,51–53

Based on the recently published guidelines in CV research, efforts should be made to prospectively collect gender-related variables as pertinent to their research hypothesis/questions and explore retrospectively available datasets using the GOING-FWD methodology.54

The gender working group of the Italian Society of Internal Medicine (SIMI), funded in 2019, have conceptualized based on the evidence available51,52 a list of variables that should be collected through questionnaire that capture gender domains in the clinical studies.53 Specifically, the gender core dataset consists of data regarding personality traits (gender identity), occupation, caregiver status, household responsibilities, condition of primary earner (gender roles), marital status, social support and discrimination (gender relations), and educational level, personal income and living area (institutionalized gender).

Possible tools to enhance inclusivity in cardiac rehabilitation

Several solutions might be available to fill the gap of lower rates in CR participation; however, first it would be beneficial to increase physicians' awareness of the essential benefits related to this strategy of prevention.10,12 Moreover, it would help to invest substantial resources in the healthcare system to ensure high-quality and high-capacity rehabilitation centres.10,12 Improvements in counselling and social support may be necessary for major attendance to therapy.

Regarding specifical sex and gender-issues that limit participation to CR, a more tailored programmes based on women attitude and needing, that may lead to an increase in CR participation, and correct the modifiable barriers, through flexibility of timetable (with both morning and afternoon sessions) and strategy to manage stress might be helpful.49 Another important issue would be to promote the knowledge, between the physicians, of the four main domains (e.g. gender identity, gender roles, gender relations, and institutionalized gender) in line with the statement recently made by a panel of experts on an open-access CR education resources to support women in

CV prevention through their participation in CR.55 As a benchmark of possible strategies, the million hearts initiative strive to prevent up to one million CV events through CR.56 Especially for women, with the aim of overcoming logistic problems, such as those related to transportation or the impossibility of leaving their houses, home-based programmes controlled by rehabilitation staff through telemedicine have been proposed and developed.57 The flexibility of this strategy allows physicians to follow the patient's progresses in a partially or completely remote way, thereby facilitating their adherence through individual management regarding location and time. Likewise, smartphone-based CR used to monitor digitally the improvements in exercise capacity, symptomatology and changes in lifestyle is a promising tool to be considered, leading to a possible additional improvement in communication between patients and CR staff.57–59 A recent meta-analysis, collecting studies carried on patients with coronary heart disease, acute coronary syndrome who underwent cardiac revascularization procedures, or valvular replacement surgery, showed a favourable adherence to CR through digitalization instead of traditional programmes.60 The support by the healthcare system is another aspect that might help. In fact, the reduction of the costs related to rehabilitation positively encourages participation in the programme. Another specific aspect is the need for searching neuropsychiatric disorders (i.e. depression and anxiety) that may hardly limit the women participation to CR programmes; in addition, the inclusion in CR programmes of exercises to manage stress or anxiety (e.g. yoga techniques and mindfulness) demonstrated to increase the CR attendance.61 Another possible solution may be to identify CR strategies more pleasant for women; for instance, it has been described that exercise programmes based on dance classes and with a high level of aggregation are usually appreciated by women.49

Finally, an international panel of experts published a women focused CV rehabilitation clinical practice guideline, aimed to better engage women in CR programmes and to provide guidance on how to deliver women-focused CR programme. As a result, 15 final recommendations for women-focused

CR have been proposed, relate to CR referral, setting, and delivery. Notably, of these recommendations, only two have a 'high' certainty of the evidence based on the grading of recommendations assessment, development, and evaluation criteria and 10 have been suggested with a strong level of recommendation,62 further supporting the need for sex and gender specific investigations.

Gaps in evidence

A profound gap in knowledge about the development of CR dynamics in the last decade still exists. For instance, in Italy, the more recent survey about the cardiac prevention and rehabilitation programmes dates to 2013.13 Here, it was highlighted that the total number of CR facilities amounted to 221 (1 for every 270 000 inhabitants), with 31.7% of programme response rate and at least 280 771 patients with an unmet need.12,23 Considering the broadening of the spectrum of CV disease for which CR has been now recommended in the most recent updates by the European Guidelines,10 the pool of potential patients has been extended, further widening the gap between supply and demand. Several issues are worth to be acknowledged regarding the difficulties to understand the gender related obstacles in ensuring gender equality and inclusivity in CV rehabilitation. Among sex-related differences, presentation of cardiac disease and comorbidities pose challenges specific to each sex. Women often exhibit atypical symptoms and are more likely to suffer from conditions like auto-immune diseases, osteoporosis and arthritis, which can complicate their participation in CR programmes.63–65 On the other hand, current society do not allow women to take care of their health properly. It is a matter of fact that women commonly face greater barriers due to caregiving responsibilities, reduced social support for physical activity, and different health beliefs. Women are often less aware of the benefits of CR and underestimate their heart disease risk.66,67 Socioeconomic factors further impact, considering that women are more likely to have lower incomes, less health insurance coverage, and greater difficulty accessing healthcare services.68 Higher prevalence of depression and anxiety among women can

hinder their participation in CR.30 Addressing these obstacles require tailored interventions that consider both biological and socio-cultural dimensions to improve CR utilization and outcomes for women (see *Table 3*).

Specific obstacles to perform research on barriers due to sex and gender in cardiovascular research

Obstacle type	**Specific obstacles**	**Reference**
Biological (sex-specific) obstacles	Atypical symptom presentation in women	Ades *et al.*,56 Joseph *et al.*,64 Angum *et al.*,65 and Sanderson and Bittner66
	Higher prevalence of comorbidities such as osteoporosis autoimmune diseases and arthritis in women	
Socio-cultural (gender-specific) obstacles	Greater caregiving responsibilities among women	Daponte-Codina *et al.*67 and Daher *et al.*68

Obstacle type	Specific obstacles	Reference
	Reduced social support for physical activity among women	
	Lower awareness of CR benefits and underestimation of heart disease risk among women	
	Lower incomes, less health insurance coverage, and greater difficulty accessing healthcare services among women	

Obstacle type	Specific obstacles	Reference

Finally, there are no specific analyses regarding the proper role of sex and gender and no definite strategies to increase women adherence to CR programme.

Conclusions

Despite its role as prevention tool to improve clinical outcomes of patients affected by CV diseases, to date CR is still underused, particularly by women. The identification of patients' obstacles to attend CR related to sex and gender differences has a non-neglectable impact. In fact, every subject should be considered beyond the biological sex in agreement with the four gender domains, to craft tailored therapies.

Every patient identifies his/her own gender, while the society considers and interacts with him/her on basis of the sex. Furthermore, the institutionalized gender might represent the distribution of power between genders in the political, educational, religious, medical, cultural, and social institutions. All that should be considered in the management of the individual to improve clinical outcomes. According to CR, possible tools to optimize patients' participation are represented by increased referral rate related to physicians' awareness of the essential benefits of CR, strengthening in healthcare system facilities, patients' information after hospital discharge, tailored rehabilitation programmes, and the use of telemedicine and telemonitoring to allow a stricter connection between CR staff and patient and to contrast socio-economic problems or familial and logistic obstacles. International scientific societies and ministerial governance should be involved in this process to reduce sex and gender inequality in CR attendance.

18. ‘Hot’ Doc? Radiation Exposure Risks of Interventionalists Aired in TV Special

n just a few short decades, the field of interventional cardiology has led to groundbreaking treatments for patients with cardiovascular and structural heart disease. But the radiation that helps operators guide their wires and place stents, not to mention the heavy lead they must don, has resulted in injury, illness, and shortened careers for many passionate physicians, a new documentary details.

Scattered Denial, which began airing this summer on PBS stations around the United States, tells the stories of these interventionalists, and while the concerns are not new, those involved say they hope the program sounds a siren within the field: protect itself in order to be sustainable.

“We have worried about the conditions in factories like GM, Chrysler, and Ford Motors. If [they] had this kind of workplace injury and did so little to protect the workers, they would be shut down,” said David Rizik, MD (HonorHealth, Scottsdale, AZ).

The documentary is Rizik’s passion project: a 2-year journey to speak with operators across the United States, from well-known faces like Society for Cardiovascular Angiography & Interventions (SCAI) president James B. Hermiller, MD, who needed emergency back surgery, to physicians who have no hair on the left side of their bodies due to close proximity to the radiation source while working. Some overcame their injuries and illnesses with time. Others were not so lucky.

Rizik estimates that over a 20-year career, a cath lab worker may have had the equivalent of 20,000 chest X-rays to the head and neck.

“Every time we step in to save a life, we are exposing ourselves to potential harmful effects of ionizing radiation,” he said. “But it’s easy to overlook the

dangers when presented with sick patients and when physicians are young and laser-focused on improving their procedural skills."

In the documentary, Robert Foster, MD (Birmingham Heart Clinic, AL), says taking radiation badges off was commonplace in his younger years despite knowing that working in a cath lab presents the greatest risk of radiation exposure of all medical specialties.

> **Many times honestly we take our badges off because we know we're going to exceed those limits, and our passion is to be in the cath lab.** Robert Foster

Also in the documentary, filmed before his death, Edward B. Diethrich, MD, who founded the Arizona Heart Institute, says he considered himself "indestructible" when it came to radiation, adding, "Obviously, I didn't know what I was talking about, did I?" As TCTMD reported, Diethrich died in 2017 from an oligodendroglioma brain tumor widely believed to have been the result of years of radiation exposure in the cath lab. While he admitted that the scientific evidence definitively tying excessive occupational radiation exposure to tissue damage is lacking, Diethrich remained convinced that his career and his cancer were closely related.

"It's absolutely difficult to prove," Rizik noted. "There's just so many Individuals who've developed these tumors, but we haven't studied it. It's essentially become anecdotal . . . because our professional obsession has not been workplace safety."

Skin Cancers and Back Problems

To TCTMD, Rizik said while the stories in the documentary are painful and personal for everyone involved, he believes they are also crucial for younger interventional cardiologists to hear and heed.

John T. Eagan Jr, MD (Cardiovascular Associates, Birmingham, AL), says he experienced years of skin cancers on the left side of his body, including his

head and neck, that were initially attributed to sun exposure. He continued to work in the cath lab like his father had done, doing 10 to 20 procedures every day. He says he attempted to use as much radiation protection as possible, “but sometimes it wasn’t practical to use complete protection in trying to take care of very sick, acutely ill cardiac patients.” The basal cell carcinomas became relentlessly frequent and by the age of 50 he had reached a point where he was needing to see a dermatologist almost daily due to new left-sided lesions.

Eagan ultimately had no choice but to leave his interventional practice to avoid further radiation exposure that he was told could be life-threatening. The abrupt shift in his career path was jarring, leaving him questioning if he could ever practice again. In time, he made the switch over to noninvasive cardiology and is at peace with the decision.

“In the cath lab, you really aren’t taught about where the radiation comes from . . . you wear your badge and it’s being monitored, but many times honestly we take our badges off because we know we’re going to exceed those limits, and our passion is to be in the cath lab,” said Foster.

He added that one of the unknowns about cath lab radiation exposure is not knowing how your body is going to react to cumulative exposure, likening the situation to patients with smoking histories who have normal arteries while others have been ravaged by their cigarette exposure.

“The cancer problem is real in that one in 25 of us will probably die of a radiation-induced cancer,” he said. A life-long runner, Foster experienced a ruptured disc in his back, which his orthopedic surgeon felt was from his 15 years of wearing heavy lead in the lab. Unwilling to give up his career at that point, Foster thought cutting back on his running might be enough to ease the strain on his back. Four years later, the disc ruptured again, paralyzing his right leg and leaving him unable to walk for about a month. This time, he made the decision to leave the cath lab for the sake of his health and his family.

Women, Cancer, and Pregnancy

Many people interviewed for the documentary said they received little to no training in radiation safety. Some like Aimee Armstrong, MD (Nationwide Children's Hospital, Columbus, OH), said they felt compelled to follow their mentors' actions, many of whom didn't like lead shields because "they got in the way" of doing their job.

In 2021, Armstrong was diagnosed with breast cancer despite having no family history of it and despite a recent normal mammogram. The tumor was in her left breast, leaving her to wonder if gaps in her lead vest at the armpit could have played a role in cumulative radiation exposure and tumor formation. As with Diethrich and others in the documentary, the source of Armstrong's cancer remains an open question and a strong motivator for her to advocate for changes in the field that protect everyone.

> **You can be pregnant in the lab, and if you take appropriate protective measures, you can have a safe pregnancy.** Celina Yong

Radiation concerns are often blamed for influencing the gender breakdown in interventional cardiology. In the United States, only 4.5% of interventional cardiologists are female, according to data from the National Cardiovascular Data Registry. In a survey of over 500 general cardiology fellows published in 2019, Celina Yong, MD, MBA (VA Palo Alto Healthcare System, CA), and colleagues found that men were significantly more interested than women in seeking a career in interventional cardiology. Looking further at those differences, they found that among other things, women were much more concerned than men about radiation exposure risk during their childbearing years. A primary motivator for women to choose the field was the presence of a female mentor or role model.

"When you look at the numbers, interventional cardiology ranks at the bottom in terms of gender representation compared to almost every field in medicine," Yong told TCTMD. During her own training, she said she felt

particularly uncertain about the topic of pregnancy while working in the lab and noted that there were few helpful data or mentors who could offer advice. A 2017 survey by the American College of Cardiology's Women in Cardiology (WIC) section illustrated the disconnect, showing that despite expressing concerns about radiation exposure during pregnancy, only about 20% of female interventional cardiologists reported using fetal badges during a pregnancy and only 24% used additional lead.

Yong said one of her first projects as an attending was creating a curriculum around this topic and making it a required lecture for trainees.

She had her first pregnancy while a general cardiology fellow, her second as an interventional cardiology fellow, and her third as an attending working in the cath lab every day, and she said it's important that radiation safety for pregnant cardiologists and those planning pregnancies be a topic for everyone in the specialty, not only to ensure safety, but also to grow the field and enrich it with talented women.

"You can be pregnant in the lab, and if you take appropriate protective measures, you can have a safe pregnancy," Yong said. She added that stories like those shared in the documentary by primarily senior interventionalists who have been in the field for decades are important for younger cardiologists to hear and "are inextricably tied to our efforts to improve diversity in the field and to provide better care for our patients."

Toward a More Stable Workforce

For Rizik, these stories and so many others in the documentary Illustrate the impact that their day-to-day work hazard has had on themselves and their families for decades.

"How we have addressed it hasn't changed in 40 years. The lead apron we wear has not changed in all that time," he said. "When [National Football League] owners were advised of the need to make changes to equipment and sideline changes, they did it to protect their athletes. We've done so little.

Why is it that doctors are the exception to the rule in terms of workplace safety?"

> **Every time we step in to save a life, we are exposing ourselves to potential harmful effects of ionizing radiation.** David Rizik

Looking back, Rizik said there can be no doubt that the interventional cardiology field has made great strides for patients, yet it is littered with tragedy for many physicians. Armstrong, who developed breast cancer, was supported through her diagnosis and treatment by her good friend Kanishka Ratnayaka, MD, a pioneer in pediatric interventional cardiac MRI. Ratnayaka died in 2021 of cancer in his 40s. Like some others in the documentary, Armstrong has high hopes that one day, low-field MRI scanning will eliminate the need for X-ray in cardiac catheterization.

Foster, despite switching to general cardiology after his ruptured discs, wasn't ready to completely give up on the field that had been his passion. With collaborators, he helped design an adjustable, portable radiation shielding system (Rampart; Rampart ic) that protects interventionalists and their technicians without requiring them to wear lead. The shield has allowed Foster to return to doing the procedures he loves and has created a sense that it is time to "switch from personal protection to community protection."

Other novel shielding systems are entering the market and offering a way to dramatically change cath lab safety dynamics. Earlier this year, Rizik presented data at CRT 2024 on a comprehensive radiation shield (Protego; Image Diagnostics) that cut radiation exposure to primary operators during coronary and structural heart procedures by more than 99% when used in combination with standard safety measures.

Rizik said getting operators to the point of being lead-free is the goal to avoid illness and injury as well as to prolong their ability to do their jobs.

“People who have been in the cath lab for 20, 30, 40 years have seen how this problem has affected themselves and their colleagues,” he said. “Potentially the interventional cardiologist is going to have a shortened career because of this. In talking to people around the country, I also found that many had sought psychiatric care because of needing to leave the cardiac catheterization laboratory.”

In a recent editorial in JSCAI, Rizik called the need for zero radiation in the cath lab a “moral imperative” as opposed to an aspirational goal.

“The more-senior interventional cardiologists who you see in this documentary have really seized this opportunity to tell their stories and the consequences they have suffered. I think it is incumbent on us to create a safer workplace for the next generations,” he said. “The solution is awareness and involvement from all stakeholders.”

Rizik and others in the documentary acknowledge that cost is a stumbling block, with hospital systems charged with buying the shielding systems and configuring labs around them.

“Ultimately, I think it will be a recruitment tool and it'll create greater job satisfaction and a happier work environment,” Rizik said. “The bottom line is we have to protect employees, and if we do that, we will create a more stable workforce.”