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1. Sex Differences in Prescription Patterns and Medication Adherence to GDMT Among Patients With Ischemic Stroke

BACKGROUND

Ischemic stroke is a leading cause of death and disability. Society guidelines recommend pharmacotherapies for secondary stroke prevention. However, the role of sex differences in prescription and adherence to guideline-directed medical therapies (GDMT) after ischemic stroke remains understudied. The aim of this study was to examine sex differences in prescription and adherence to GDMT at 1-year after ischemic stroke in a cohort of commercially insured patients.

METHODS

Using the Truven Health MarketScan database from 2016-2020, we identified patients admitted with ischemic stroke. GDMT was defined as any statin, antihypertensive, and anticoagulant prescription within 30-days after discharge. Medication adherence was estimated using the proportion of days covered (PDC) at 1-year. PDC <0.80 was used to define non-adherence. A multivariable model adjusting for covariates was performed to identify the factors associated with non-adherence at 1-year. This analysis was restricted to new users of GDMT.

RESULTS

Among 155220 patients admitted with acute ischemic stroke during the study period, 15,919 met the inclusion criteria. The mean age was 55.7 years, and 7,701 (48.3%) were women. Women were less likely prescribed statins (58.0% vs 71.8%), and antihypertensives (27.7% vs 41.8%). In this subset of patients with atrial flutter/fibrillation, women were also less likely prescribed anticoagulants (41.2% vs 45.0%). Women were more likely to be non-adherent (i.e., PDC <0.80) to statins (47.3% vs 41.6%, P<0.0001), antihypertensives (33.3% vs 32.2%, P=0.005), and the combination of both

(49.6% vs 45.0%, P=0.003). On multivariable analysis, women were likely to be non-adherent to GDMT at 1-year (odds ratio 1.23, 95% confidence interval 1.08-1.41).

CONCLUSIONS

In this real-world analysis of commercially insured patients with ischemic stroke, women were less likely initiated on GDMT within 30 days after discharge. Women were more likely to be non-adherent to statins and antihypertensive agents at 1-year. Future efforts and novel interventions are needed to understand the reasons and minimize these disparities.

2. What is the role of sex and gender in the future of precision cardiology?

Precision medicine is an ongoing cultural revolution in contemporary medicine, involving research and clinical practice at the same time (Figure 1). In contrast to the traditional reductionist approach, precision medicine aims to broaden the practical definition of disease beyond the mere association of signs and symptoms, to include the unique characteristics of individual patients, such as their genetic background, their history of environmental exposure, and their social interactions.1 The idea that the optimal strategy to restore and/or preserve the optimal health status should be tailored on individual characteristics is not novel and can be traced back in the ancient European humoral theory or the traditional Chinese medicine.2 However, during the 19th and 20th centuries, the embedding of the scientific method in medical research has favoured the adoption of a simplified approach, leading to immeasurable advances in medical knowledge and in the effectiveness of clinical interventions.

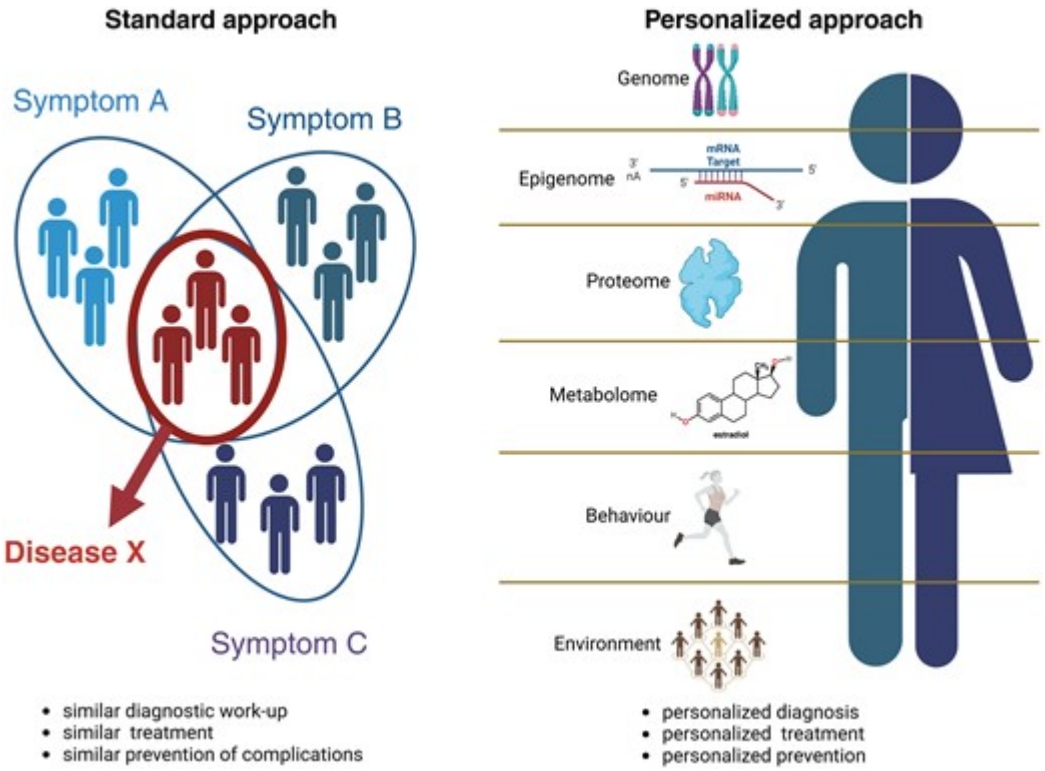

Figure 1

Compared with the classical approach to medicine, based on a statistical definition of disease, precision medicine encompasses a personalized approach to diagnosis, treatment, and prevention. This envisages the comprehensive evaluation of different factors, ranging from a genetic level (genome) to an environmental and social level (exposome). Sex and gender differences express at each of these levels and should be considered when implementing a personalized approach to health and disease. Created with BioRender.com.

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The current epidemiological landscape, largely populated by chronic, non-communicable diseases with multifactorial origin, has highlighted the shortcomings of this approach. In the field of cardiovascular prevention, for instance, the evidence of a residual risk after optimization of all atherosclerotic risk factors underscores the relevance of the cumulative overtime effect of risk factors that should, therefore, be managed

individually long before they reach the usually accepted risk thresholds, based on individual susceptibility to one or more specific risk factors. This can only be possible by the use of novel predictive tools, which allow tailored interventions using a broad range of potential predictors. Nowadays, modern technology has provided us with the tools to investigate the individual susceptibility to cardiovascular disorders and risk factors in depth, using a multi-omics approach; at the same time, advances in information technology and artificial intelligence allow us to integrate this heterogeneous amount of data with traditional clinical parameters.3

Under this perspective, the integration of genomic and epigenomic information could provide novel instruments for a refined risk prediction.

Compared with other fields of modern medicine, such as oncology and rheumatology, acquisitions of precision medicine have a smaller practical application in cardiology and vascular medicine. This gap is mainly due to the terrific efficacy of traditional pharmacological and non-pharmacological interventions in the management of cardiovascular diseases (CVDs).

At the same time, the weight of sex and gender disparity is emerging as a strong hindrance in modern management of cardiology and vascular medicine. Accumulating evidence suggests that, at the present time, CVDs are under-diagnosed and under-treated in women compared with men, and women are currently under-represented in epidemiological studies and clinical trials. For instance, women with non-ST-elevated myocardial infarction tend to receive fewer percutaneous coronary interventions.4 As a result, women may report higher mortality rates following coronary artery disease, even when coronary artery bypass graft is employed.5 Whether this disparity results from a cultural bias or from an epidemiological drift in CVDs is still a matter of debate. However, there is nowadays an increasing interest around sex differences in CVD, leading to the development of novel sex-specific prognostic tools, as well as novel acquisitions about biological determinants of sex differences.6,7 Indeed, the intrinsic complexity of biological sex is often overlooked in clinical research and sex differences are

commonly reconducted to the pleiotropic effects of steroid sex hormones. Biological sex is instead a complex phenotype, determined by the concurrent effect of genomic, epigenomic, anatomic, hormonal, and metabolic factors. On top of this, social constructs and economic differences, collectively named as 'gender' features, contribute to the different health status between men and women.

For instance, several genetic variants associated with the risk of developing CVDs show a sex-biased impact, influencing disease patterns, responses to treatment, and outcomes in a sex-specific manner.8 Furthermore, the two sexes differ from one another because of variations in gene expression independent from the underlying DNA sequence (epigenetic differences). Non-coding RNAs, including microRNAs and long non-coding RNAs, are integral components of epigenomic regulation, influencing gene expression without coding for proteins. Moreover, they are involved in the preservation of the chromatin structure, regulation of histone modifications, and control of transcriptional activity, thus playing key roles in cardiovascular health and disease.9

Micro-array analyses of human organ tissues revealed sex differences in microRNA transcriptome in both normal and diseased heart, with potential impact on susceptibility to CVD incidence and progression. Sex differences in the expression of non-coding RNAs are due to two main factors: (i) numerous gene promoters contain oestrogen-responsive elements, where the binding of oestrogen induces the expression of miRNAs; (ii) the X chromosome encodes 118 microRNAs, most of which are grouped into six regional clusters. Several of these X-linked microRNAs have been reported to escape X chromosome inactivation, resulting in higher expression levels in specific cell types such as endothelial cells, vascular smooth muscle cells, and cardiomyocytes. This sex-specific modulation of cell function can lead to different pathophysiological regulatory processes between men and women and may specifically explain sex-specific cardiovascular pathological features in women, such as in heart failure with preserved ejection fraction.10

Unravelling the complex interaction of sex and gender in CVDs requires a 'precision medicine' approach, as multiple levels of complexity need to be analysed. Could the expanding research in sex and gender differences help precision medicine grow within the field of cardiology and cardiovascular research?

3. Women With ACS Less Likely to Receive CV Follow-Up

Women are less likely than men to receive appropriate cardiovascular follow-up and medication prescriptions after being hospitalized for acute coronary syndromes (ACS), according to a study in the *Journal of the American Heart Association*.

Researchers analyzed the data of patients with ACS within the Veterans Affairs (VA) Health System and the VA Clinical Assessment, Reporting, and Tracking Program.

All participants had an admission and discharge for ACS within the VA Healthcare System from October 1, 2015, to September 30, 2022. The primary clinical outcomes were mortality at 30 days and 1 year.

The cohort included 74,129 men (96.96%) and 2327 women (3.04%), with a median follow-up of 766 days (IQR, 208-1553). Propensity matching identified 6765 men (74.67%) and 2295 women (25.33%), with a median follow-up of 1003 days (IQR, 353.75-1748).

A lower proportion of women were prescribed most cardiovascular medications, except for angiotensin receptor blockers, before presenting with ACS. For postdischarge medication prescriptions, a decreased proportion of women received prescriptions for statins, high-intensity statins, β blockers, or P2Y12 inhibitors (all P <.01).

These data suggest an opportunity to improve the posthospitalization management of cardiovascular disease regardless of sex.

No association was observed between sex and Bleeding Academic Research Consortium 3a in a hospital visit (odds ratio [OR], 1.00; 95% CI, 0.981-

1.020) or readmission within 30 days of discharge (OR, 0.989; 95% CI, 0.971-1.008) for those who survived 30 days or longer. Women had a significantly reduced hazard of death (15.9%) within 1 year of discharge (hazard ratio [HR], 0.841; 95% CI, 0.747-0.948; P <.01). The HR for 30-day mortality for women was 0.886 (95% CI, 0.746-1.052; P =.17).

Women had significantly reduced cardiology follow-up, with a 14.2% lower hazard of follow-up within 30 days (HR, 0.858; 95% CI, 0.794-0.928; P <.01) and a 10.9% lower hazard of follow-up within 1 year (HR, 0.891; 95% CI, 0.842-0.943; P <.01).

No significant difference occurred in the hazard of women who had 30-day internal medicine follow-up and 1-year internal medicine follow-up compared with men.

Among several limitations, the data were analyzed in an observational manner, clinical characteristics such as left ventricular ejection fraction were not universally available, and the population was from the VA Healthcare system.

"These data suggest an opportunity to improve the posthospitalization management of cardiovascular disease regardless of sex," the researchers wrote.

4. Automated Breast Arterial Calcification Score Is Associated With Cardiovascular Outcomes and Mortality

Introduction

Cardiovascular disease (CVD) remains the leading cause of death in women despite significant advances in cardiovascular diagnostics and treatments.**1** Delays in diagnosis and treatment, as well as undertreatment, contribute to morbidity and mortality.**2** This is further exacerbated by under-representation of women in cardiovascular clinical trials and lack of sex-specific screening tools.**3** Efficient and effective methods to broadly screen women for CVD risk are sorely needed.

Breast arterial calcification (BAC), an incidental finding on mammograms, has emerged as a sex-specific biomarker for atherosclerotic cardiovascular disease (ASCVD) that offers the potential for personalized risk stratification.**4** The prevalence of mammographic BAC increases with age, occurring in 10% of women at age 40 but in up to 50% by age 80 years.**5-7** In semiquantitative analysis using radiologist assessments, high-grade or severe BAC was rare in younger women, but approached 14% by age 70 years.**8**

Gleaning information from an imaging study beyond its original intent is not new; analogous to BAC on mammography is coronary artery calcifications (CACs) seen on chest computed tomography obtained for noncardiac purposes.**9** BAC has tremendous appeal for cardiovascular risk stratification because it is noninvasive, comes at no additional cost or radiation, and the majority of women over the age of 40 years already undergo annual screening mammography for breast cancer.**10**

Multiple studies have found significant associations between the presence of BAC and prevalent CVD.**4** It is postulated that BAC represents lifetime exposure to risk factors related to arterial stiffening, which increases the risk of CVD through both coronary and noncoronary mechanisms (ie, heart failure [HF] and stroke).**11** However, routine clinical use of BAC has not been adopted due to a lack of outcomes studies as well as technological challenges in measuring and reporting BAC.**4** Currently, there is no consensus recommendation on the inclusion or standardized reporting of BAC, and American College of Radiology guidelines on breast imaging classifies reporting of vascular calcifications as optional.**12**,**13** However, in 2023, the Canadian Society of Breast Imaging took a progressive stance, advocating for standardized reporting of BAC in mammogram reports.**14**

Moreover, most BAC studies are limited to the binary presence or absence of BAC, and thus are blind to the severity or burden of BAC. Few studies measure or categorize BAC by severity and there is significant heterogeneity in classification.**7** The purpose of this study was to evaluate not only the

association of BAC presence with CVD risk factors and hard clinical outcomes in a large population but also to validate the utility of a novel automated, artificial intelligence (AI) algorithm for personalized BAC quantification.

Methods

Study population

This single-center retrospective study included women between the ages of 40 and 90 years who underwent screening digital mammography between 2007 and 2016 at the University of California-San Diego Health. For each subject, only the index mammogram was analyzed. All protocols were approved by the Institutional Review Board (IRB #170154).

Evaluation of BAC

BAC was quantified using a validated, proprietary investigational software (cmAngio, CureMetrix) based on a deep neural, AI network, and previously trained with an 80:20 split using over 34,000 2D full-field digital mammograms and digital breast tomosynthesis mammograms obtained from multiple sites across 13 health care facilities in Australia, Brazil, and the United States (not including University of California-San Diego Health).

As a standard, 4 full-field digital mammograms or digital breast tomosynthesis images from each participant were used. The software cmAngio assesses screening mammography images and feeds them through the deep learning model to identify regions of interest within the breast. These regions correspond to areas that the algorithm suspects to have a high probability of BAC. From these identified regions, local and global imaging features such as density, contrast, and other physical dimensions are combined to determine the presence and severity of BAC. This process is applied to each of the 4 standard screening mammography images. Following these calculations, each image is assigned a score between 0 and 100 corresponding to the severity of the BAC finding(s), with 0 representing

no BAC and 100 representing the highest percentile of BAC. To balance the algorithm's false positive and false negative rate, all image-level scores <5 are floored to 0. The patient-level score (or BAC score) is the mean of the threshold image-level scores across all 4 views. As such, BAC presence was defined as a mean BAC score ≥5. BAC was evaluated as a binary variable (presence vs absence), continuous variable (BAC score 0-100), and quartile groups (first-fourth). Scores were distributed by severity into the following groups: first quartile [score 1-25], second quartile [score 26-50], third quartile [score 51-75], and fourth quartile [score 76-100].

During development, each case was reviewed by 2 of 11 Mammography Quality Standards Act-certified radiologists. The performance of the software for detecting BAC, as assessed by area under the receiver operating characteristic curve was 0.98, with a sensitivity of 94% and a specificity of 96%. The software is cleared for BAC detection by the Food and Drug Administration and has been deployed in investigational clinical settings with Institutional Review Board approval.

Clinical data and outcomes

All clinical data including baseline characteristics and outcomes were collected using electronic health records (EHRs) and International Classification of Diseases (ICD)-10 codes, which are provided in **Supplemental Table 1**. All incident diagnoses occurred at least 6 months after the index mammogram and until death or the censoring date of December 31, 2020. The primary outcome was all-cause mortality. Secondary outcomes included acute myocardial infarction (MI), HF, stroke, and a cardiovascular composite outcome (MI, HF, stroke, and mortality). Stroke (cerebrovascular disease) included ischemic and hemorrhagic stroke. Those with baseline MI, HF, or stroke were excluded from the relevant outcome analyses, including the composite outcome. Additionally, in a sensitivity analysis, all participants with baseline ASCVD were excluded to reassess the associations. ASCVD was defined by the following ICD-10

diagnoses: ASCVD, coronary artery disease (CAD), peripheral arterial disease (PAD), HF, and/or cerebrovascular disease.

Analyses and statistical methods

Continuous variables were reported either as mean ± SD or as median with (IQR) as appropriate based on normality of distribution assessed by Shapiro-Wilk test. Categorical variables were expressed as counts with percentages. Variables were compared using the unpaired Student *t*-test, Mann-Whitney test, and Fisher's exact test, as appropriate. Proportional hazards assumptions were tested for all outcomes to verify modeling assumption. Furthermore, Schoenfeld residual plots were generated for confirmation. Kaplan-Meier survival curves (plotted with 95% CIs), cumulative incidence plots (as appropriate), and Cox proportional hazards regression analyses were used to determine associations between BAC (as a binary and continuous variable) and clinical outcomes, while adjusting for variables at the time of mammogram (age, race/ethnicity, smoking status, systolic blood pressure, diastolic blood pressure, total cholesterol, low-density lipoprotein [LDL] cholesterol, diabetes mellitus, and a history of CVD or chronic kidney disease [CKD]).

Age was continuous and measured in years. Smoking status was categorical and defined as current, former, never, or unknown. Systolic and diastolic blood pressures were continuous and measured in mm Hg. Total cholesterol and LDL cholesterol were continuous and measured in mg/dL. For other covariates, diabetes mellitus and CKD were defined by the associated ICD-10 code (**Supplemental Table 1**). CVD was defined as an ICD-10 code for any of the following: ASCVD, MI, CAD, HF, and/or stroke (cerebrovascular disease). For those without covariate data from the time of the index mammogram, imputation was performed to account for these missing data. Data were imputed by training a nearest neighbor multiple-imputation model in Python to predict missing variables using the 10 nearest neighbors based on the collected diagnosis codes, age, ethnicity, smoking status, blood pressure (systolic and diastolic), and cholesterol (total and LDL).

Forest plots were created to assess the association between BAC and outcomes, stratified by subgroups of baseline characteristics. Tails represent 95% CIs. All reported *P* values were 2-sided with a value of <0.05 considered statistically significant. Statistical analyses and figures were completed using Python 3.11.5 with packages including Pandas 2.1.0 and SciPy 1.11.2.

Results

Study population

There were 21,438 screening mammograms obtained between 2007 and 2016. Of these, 1,546 were excluded for age and 1,800 were excluded for not being the index study. Therefore, 18,092 women with index mammograms were included in the study (**Figure 1**). Among the 18,092 women included, the mean age was 56.8 ± 11.0 years with prevalent CVD risk factors of diabetes (13%), hypertension (36%), and hyperlipidemia (40%) (**Table 1**). BAC was present in 4,223 (23%). BAC was more prevalent among women who were older, Black or Hispanic, diabetic, hypertensive, with a history of ASCVD or CKD, and taking statins and/or antihypertensive medications. BAC was less prevalent in current smokers. Among those with BAC, the median score was 15 (IQR: 4-50). Scores were distributed by severity into the following quartile groups: first quartile [score 1-25], n = 2,552 (60.4%); second quartile [score 26-50], n = 643 (15.2%); third quartile [score 51-75], n = 509 (12.1%); and fourth quartile [score 76-100], n = 519 (12.3%). Correspondingly, those with a higher BAC score were more likely to be older, diabetic, hypertensive, having a history of CVD, CKD or hyperlipidemia, and taking statin and antihypertensive medications. (**Supplemental Table 2**). Additionally, details on imputation and missing covariate data are presented in **Supplemental Table 3**.

Participant Flow Diagram

After exclusions for age and non-index mammograms, there were 18,092 unique women with index mammograms included in this study.

Table 1Baseline Participant Characteristics by Presence of Breast Arterial Calcification	**Total (N = 18,092)**	**BAC Present (n = 4,223; 23%)**	**BAC Absent (n = 13,869; 77%)**	***P* Value**
Age, y	56.8 ± 11.4	65.2 ± 11.6	54.2 ± 10.0	<0.001
Race/ethnicity				
Caucasian	11,319 (62.6)	2,617 (62.0)	8,702 (62.7)	0.38
Black/African American	907 (5.0)	241 (5.7)	666 (4.8)	0.02
Hispanic/Latino	1,694 (9.4)	455 (10.8)	1,239 (8.9)	<0.001
Asian/Pacific Islander	2,321 (12.8)	496 (11.8)	1,825 (13.2)	0.02
Other	1,851 (10.2)	414 (9.8)	1,437 (10.4)	0.31
Diabetes	2,267 (12.5)	730 (17.3)	1,537 (11.1)	<0.001
Hypertension	6,529 (36.1)	2,179 (51.6)	4,350 (31.4)	<0.001
Hyperlipidemia	7,256 (40.1)	2,071 (49.0)	5,185 (37.4)	<0.001
History of CVD	874 (4.8)	424 (10.0)	450 (3.2)	<0.001
History of CKD	802 (4.4)	358 (8.48)	444 (3.2)	<0.001
Current smoking	834 (4.6)	134 (3.17)	700 (5.1)	<0.001
Never smokers	9,245 (51.1)	2,046 (48.5)	7,199 (52.6)	<0.001
Systolic blood pressure, mm Hg	123 (21)	128 (20)	122 (20)	<0.001
Total cholesterol, mg/dL	198 (52)	194 (53)	199 (51)	<0.001

Table 1Baseline Participant Characteristics by Presence of Breast Arterial Calcification	**Total (N = 18,092)**	**BAC Present (n = 4,223; 23%)**	**BAC Absent (n = 13,869; 77%)**	***P* Value**
Statin use	3,947 (21.8)	1,430 (33.9)	2,517 (18.1)	<0.001
Antihypertensive use	3,498 (19.3)	1,313 (31.1)	2,185 (15.8)	<0.001

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

BAC = breast arterial calcification; CKD = chronic kidney disease; CVD = cardiovascular disease.

Clinical outcomes

Over a median follow-up for mortality of 4.8 years (IQR: 4.2 years), there were 329 deaths in those with BAC (7.8%) and 313 deaths in those without BAC (2.3%) ($P < 0.001$) (**Table 2**). Over a median follow-up for the composite outcome of 4.3 years (IQR: 4.3 years), there were 500 events in those with BAC (12.4%) and 582 events in those without BAC (4.3%) ($P < 0.001$). Stroke, MI, and HF were more frequently observed in those with BAC present, although the competing risk of death precludes statistical comparison. Kaplan-Meier Plots for mortality and the composite outcome are shown in **Figure 2**, which demonstrate a significantly increased risk of outcomes in those with BAC ($P < 0.001$ for each). Additionally, for HF, over a median follow-up of 3.0 years (IQR: 4.6 years), there were 154 events in those with BAC (3.7%) and 144 events in those without BAC (1.0%) ($P < 0.001$). For MI, over a median follow-up of 3.3 years (IQR: 3.9 years), there were 36 events in those with BAC (0.9%) and 47 events in those without BAC (0.3%) ($P < 0.001$). Lastly, for stroke, over a median follow-up of 3.0 years (IQR: 4.7 years), there were 110 events in those with BAC (2.7%) and 149 events in those without BAC (1.1%) ($P < 0.001$). Cumulative incidence plots for individual outcomes of stroke, MI, and HF are shown in **Supplemental**

Figure 1, which also demonstrate significantly increased risk in those with BAC ($P < 0.001$ for each outcome).

Table 2Clinical Outcomes by Breast Arterial Calcification Presence	**Total (N = 18,092)**		**BAC Present (n = 4,223)**		**BAC Absent (n = 13,869)**		***P* Value**
Myocardial infarction	18,051	83 (0.5%)	4,204	36 (0.9%)	13,847	47 (0.3%)	
Heart failure	17,911	298 (1.7%)	4,119	154 (3.7%)	13,792	144 (1.0%)	
Stroke	17,914	259 (1.5%)	4,138	110 (2.7%)	13,776	149 (1.1%)	
Mortality	18,092	642 (3.6%)	4,223	329 (7.8%)	13,869	313 (2.3%)	<0.001
Composite outcomea	17,720	1,082 (6.1%)	4,031	500 (12.4%)	13,689	582 (4.3%)	<0.001

Values are N or n (%).

Abbreviations as in **Table 1**.

a The cardiovascular composite outcome included acute myocardial infarction, heart failure, stroke, and mortality.

In multivariable analysis, women with BAC present had a significantly higher risk of mortality (adjusted HR [aHR]: 1.49 [95% CI: 1.33-1.68], $P < 0.001$) and the composite outcome (aHR: 1.57 [95% CI: 1.42-1.74], $P < 0.001$), compared to those without BAC (**Table 3**). Exclusion of those prescribed statin therapy (n = 3,947) did not materially affect the results: mortality aHR 1.45 (95% CI: 1.29-1.63), $P < 0.001$ and the composite outcome aHR 1.53 (95% CI: 1.38-1.69), $P < 0.001$ (**Table 3**). After excluding those with any baseline ASCVD, results were essentially unchanged (**Table 3**). For example, for the mortality outcome, exclusion of 758 participants

with baseline ASCVD still led to a significant difference (aHR: 1.44 [95% CI: 1.28-1.62]; *P* < 0.001). For the composite outcome, exclusion of those with baseline ASCVD, CAD, and PAD (n = 399) did not significantly alter the results (aHR: 1.50 [95% CI: 1.35-1.66]; *P* < 0.001) (**Table 3**).

Table 3Association of Breast Arterial Calcification Presence and Clinical Outcomes	**Mortality HR (95% CI)**	***P* Value**	**Composite Outcomea HR (95% CI)**	***P* Value**
Among all participants	(n = 642/18,092)		(n = 1,082/17,720)	
Model 1	1.70 (1.52-1.90)	<0.001	1.92 (1.74-2.11)	<0.001
Model 2	1.58 (1.41-1.77)	<0.001	1.67 (1.51-1.84)	<0.001
Model 3	1.49 (1.33-1.68)	<0.001	1.57 (1.42-1.74)	<0.001
Excluding those prescribed statins	(n = 400/14,145)		(n = 739/14,145)	
Model 3	1.45 (1.29-1.63)	<0.001	1.53 (1.38-1.69)	<0.001
Excluding those with baseline ASCVDb	(n = 565/17,334)		(n = 1,025/17,321)	
Model 3	1.44 (1.28-1.62)	<0.001	1.50 (1.35-1.66)	<0.001

ASCVD = atherosclerotic cardiovascular disease.

a Composite outcome: acute myocardial infarction, heart failure, stroke, and mortality.

b An additional 758 participants with any baseline ASCVD were excluded for the mortality outcome and an additional 399 participants with specific baseline conditions not already accounted for were excluded for the composite outcome. Model 1: unadjusted. Model 2: adjusted for age and race/ethnicity. Model 3: adjusted for age, race/ethnicity, systolic blood pressure, diastolic blood pressure, diabetes, total cholesterol, low-density

lipoprotein cholesterol, history of cardiovascular disease, history of chronic kidney disease, and smoking status.

When BAC was quantified and analyzed as a continuous score, each 10-point increase in the BAC score was significantly and independently associated with higher risk for adverse outcomes: mortality (aHR: 1.08 [95% CI: 1.06-1.11]; *P* < 0.001)and composite outcome (aHR: 1.08 [95% CI: 1.06-1.10]; *P* < 0.001) (**Table 4**). After excluding those on statin therapy, results again were unchanged: mortality (aHR: 1.01 [95% CI: 1.007-1.013]; *P* < 0.001) and the composite outcome (aHR: 1.01 [95% CI: 1.008-1.013]; *P* < 0.001). After excluding those with baseline ASCVD, results again remained significant for both mortality (aHR: 1.01 [95% CI: 1.006-1.011]; *P* < 0.001) and the composite outcome (aHR: 1.01 [95% CI: 1.007-1.011]; *P* < 0.001) (**Table 4**).

Table 4Association of the Breast Arterial Calcification Score and Clinical Outcomes	**Mortality aHR (95% CI)**	***P* Value**	**Composite Outcomea aHR (95% CI)**	***P* Value**
Among all participants	(n = 642/18,092)		(n = 1,082/17,720)	
BAC negative, n = 13,869	Referent	-	Referent	-
Per 10-point BAC score increase	1.08 (1.06-1.11)	**<0.001**	1.08 (1.06-1.10)	**<0.001**
First quartile [score 1-25], n = 2,552	1.22 (1.06-1.41)	**0.006**	1.26 (1.11-1.43)	**<0.001**
Second quartile [score 26-50], n = 643	1.44 (1.13-1.85)	**0.004**	1.74 (1.42-2.13)	**<0.001**
Third quartile [score 51-75], n = 509	1.69 (1.33-2.14)	**<0.001**	1.83 (1.49-2.25)	**<0.001**
Fourth quartile [score 76-100], n = 519	2.27 (1.81-2.85)	**<0.001**	2.30 (1.88-2.82)	**<0.001**

Table 4Association of the Breast Arterial Calcification Score and Clinical Outcomes	**Mortality aHR (95% CI)**	***P* Value**	**Composite Outcomea aHR (95% CI)**	***P* Value**
Excluding those prescribed statins	(n = 400/14,145)		(n = 739/14,145)	
BAC negative, n = 11,352	Referent	-	Referent	-
Per 10-point BAC score increase	1.01 (1.007-1.013)	**<0.001**	1.01 (1.008-1.013)	**<0.001**
First quartile [score 1-25], n = 1,838	1.27 (1.07-1.51)	**0.007**	1.25 (1.07-1.46)	**0.006**
Second quartile [score 26-50], n = 390	1.48 (1.07-2.06)	**0.018**	1.72 (1.31-2.27)	**<0.001**
Third quartile [score 51-75], n = 295	1.58 (1.13-2.19)	**0.007**	1.69 (1.26-2.25)	**<0.001**
Fourth quartile [score 76-100], n = 270	2.53 (1.81-3.53)	**<0.001**	2.61 (1.97-3.47)	**<0.001**
Excluding those with baseline ASCVDb	(n = 565/17,428)		(n = 1,025/17,428)	
BAC negative, n = 13,540	Referent	-	Referent	-
Per 10-point BAC score increase	1.01 (1.006-1.011)	**<0.001**	1.01 (1.007-1.011)	**<0.001**
First quartile [score 1-25], n = 2,414	1.21 (1.05-1.40)	**0.007**	1.15 (0.97-1.36)	0.111
Second quartile [score 26-50], n = 593	1.39 (1.09-1.78)	**0.008**	1.34 (0.98-1.83)	0.071
Third quartile [score	1.59 (1.26-	**<0.001**	1.62 (1.15-	**0.006**

Table 4Association of the Breast Arterial Calcification Score and Clinical Outcomes	**Mortality aHR (95% CI)**	***P* Value**	**Composite Outcomea aHR (95% CI)**	***P* Value**
51-75], n = 459	2.01)		2.29)	
Fourth quartile [score 76-100], n = 422	2.20 (1.75-2.75)	**<0.001**	2.14 (1.53-3.00)	**<0.001**

aHR = adjusted HR; other abbreviation as in **Table 3**.

a Composite outcome: acute myocardial infarction, heart failure, stroke, and mortality.

b An additional 758 participants with any baseline ASCVD were excluded for the mortality outcome and an additional 399 participants with specific baseline conditions not already accounted for were excluded for the composite outcome. All data from the multivariable-adjusted model (Model 3), which adjusted for age, race/ethnicity, systolic blood pressure, diastolic blood pressure, diabetes, total cholesterol, low-density lipoprotein cholesterol, history of CVD, history of chronic kidney disease, and smoking status.

When assessed by BAC score quartiles, there was a significantly higher risk in a consistently graded manner for both mortality and the composite outcome (**Figure 3**), even after adjustment for cardiovascular risk factors (**Table 4**). After excluding those on statin therapy, there were no significant differences (**Table 4**). After excluding those with baseline ASCVD, similar results were seen for mortality, though for the composite outcome, the graded association only reached statistical significance starting with the third quartile (**Table 4**).

Similar associations were also seen for HF and stroke, though results for MI (only 83 incident events) did not reach statistical significance (**Supplemental Figure 2**, **Supplemental Tables 4** and **5**) of BAC. Time

points of 208 weeks and 468 weeks are indicative of approximately 4 years and 9 years, respectively.

Breast arterial calcification and clinical outcomes among subgroups

BAC prediction for mortality and the composite cardiovascular outcome significantly varied by age, systolic blood pressure, total cholesterol, LDL cholesterol, smoking, and diabetes (*P* interaction <0.001 for each). Additionally, prediction significantly varied by history of CVD for mortality (*P* interaction <0.001) and the composite outcome (*P* interaction 0.009). While prediction also significantly varied by history of CKD for mortality (*P* interaction = 0.004), it did not for the composite outcome (*P* interaction = 0.16). Kaplan-Meier plots for mortality and the composite outcome stratified by age groups (**Figure 4**) demonstrate a significant separation of curves for women aged 40 to 59 and 60 to 74 years of age (*P* < 0.001) but not for those aged 75 to 90 years (morality, *P* = 0.10; composite, *P* = 0.05).

Association of Breast Arterial Calcification and Mortality and Cardiovascular Composite Outcome Stratified by Age Groups

Risk for mortality (A to C) and the cardiovascular composite outcome (D to F) by breast arterial calcification (BAC) presence/absence. Risk for both outcomes significantly varied by BAC status among women aged 40 to 59 years (A and D) and those aged 60 to 74 years (B and E) (*P* < 0.001 for each); however, among women aged 75 to 90 years (C and F), there was no significant difference in risk for either outcome by BAC status. The composite outcome included acute myocardial infarction, heart failure, stroke, and mortality. Time points of 208 weeks and 468 weeks are indicative of approximately 4 years and 9 years, respectively. BAC = breast arterial calcification; BAC+ = presence of BAC; BAC− = absence of BAC.

Forest plots demonstrating aHRs for outcomes by stratification of baseline characteristics are shown in **Figure 5**. When stratified by age groups, and after accounting for traditional risk factors, those in the youngest age group of 40 to 59 years had the highest residual risk associated with BAC

(mortality: aHR: 1.51; 95% CI: 1.22-1.87; composite outcome: aHR: 1.52; 95% CI: 1.25-1.85). There remained significantly increased risk associated with BAC beyond traditional risk factors for women aged 60 to 74 years (mortality: aHR: 1.26; 95% CI: 1.06-1.50; composite outcome: aHR: 1.36; 95% CI: 1.18-1.58) but not among those aged 75 to 90 years (mortality: aHR: 1.19; 95% CI: 0.91-1.54; composite outcome: aHR: 1.23; 95% CI: 0.98-1.55). When stratified by other baseline characteristics, including systolic blood pressure and diabetes, the association between BAC and future cardiovascular events remained robust, even after accounting for traditional risk factors (**Figure 5**).

Association of Breast Arterial Calcification and Mortality and Cardiovascular Composite Stratified by Baseline Characteristics

Adjusted HRs for (A) mortality and (B) the cardiovascular composite outcome by breast arterial calcification (BAC) presence vs absence are presented. The composite outcome included acute myocardial infarction, heart failure, stroke, and mortality. HRs presented were adjusted for age, race/ethnicity, systolic blood pressure, diastolic blood pressure, diabetes, total cholesterol, low-density lipoprotein cholesterol, smoking status, and history of cardiovascular disease, history of chronic kidney disease. BAC = breast arterial calcification; BAC+ = presence of BAC; BAC− = absence of BAC.

Discussion

In this large, retrospective study, both the presence and quantity of BAC were significantly associated with all-cause mortality and the CVD composite outcome, even after adjusting for established cardiovascular risk factors. The prevalence of BAC was 23%, which constitutes a substantial proportion of women (mean age of 56.8 years) undergoing routine screening mammography. To our knowledge, this is the first study to demonstrate a significant, independent relationship between a quantitative BAC score and all-cause mortality or a CVD composite outcome. Indeed, each 10-point increase as well as sequential quartiles of the BAC score were significantly

associated with higher risk of mortality and adverse cardiovascular outcomes, highlighting the potential utility of BAC quantification for personalized risk assessment (**Central Illustration**).

Association of Automated Breast Arterial Calcification Scores With Cardiovascular Outcomes and Mortality

Prior studies have evaluated the association of BAC using a binary or a semiquantitative approach (such as absence, slight, moderate, and severe intensity) with CVD outcomes.**4**,**15** In the present study, BAC was quantified using an automated method driven by a trained deep neural AI network, recently validated with high diagnostic performance.**16** Other machine learning techniques have been developed for BAC quantification, including a densitometry method, and have been validated prospectively.**17** Such studies have assessed methods of BAC quantification, though await association with clinical outcomes.**18-20** The findings in our study support the efficacy of assessing both BAC presence and a quantitative BAC score to improve risk assessment for mortality and CVD outcomes in women undergoing screening mammography. With the advent of AI in medical imaging, automated, quantitative BAC assessment may facilitate seamless integration into clinical workflow and allow personalized risk assessment.

Importantly, this study also demonstrates the association of BAC with CVD outcomes and mortality even among subgroups not already known to be "high risk," including younger women, nonsmokers, and those without diabetes, hypertension, hyperlipidemia, CKD, or known CVD. We found that BAC was most predictive of future events among those in the youngest age group of 40 to 59 years, though BAC was also an independent predictor among women ages 60 to 74 years. Our results are concordant with those of Minssen et al**21** who found that the diagnostic accuracy (~ 84%) for BAC with CACs was the highest in patients under the age of 60 years. Results from this study and others suggest that BAC may develop at an earlier age than other traditional cardiovascular risk factors, and thus could serve as

an early biomarker of underlying ASCVD risk.**22** These findings are important since they suggest that early risk stratification with BAC in younger women may help identify new candidates for lifestyle modification and preventative therapies and may ultimately help improve their outcomes. Moreover, we find that quantifying BAC allows us to better stratify risk with a graded association for both mortality and the composite outcome. Thus, simply reporting BAC presence or absence is insufficient and leaves valuable information underutilized.

Even with engagement from cardiologists and patients, the success of BAC implementation hinges on buy-in and education of the radiology community. A survey of the members of the Society of Breast Imaging found that 85% were aware of the association of BAC with CVD, but only 15% routinely included BAC data on mammogram reports.**6** One of the major barriers to universal BAC reporting is the lack of radiology society guidelines on reporting and appropriate use of BAC.**6**,**9** Automated quantification and reporting methods for BAC will be critical to ensure that the current radiology workflow is not compromised.**11** Therefore, it will be important for cardiologists to advise and collaborate with the breast imaging community to develop clear BAC reporting guidelines and apply automated quantification tools into clinical workflow.

If the development and implementation of BAC can follow a similar pathway as CACs, BAC may someday be used to improve CVD risk stratification beyond current tools such as the pooled cohort equation, the ASCVD Risk Score, and the Framingham Risk Score. Reclassification of risk will help identify those who will benefit from more aggressive lifestyle modifications and medical therapy (ie, statins, antihypertensives).

Recently, the MINERVA (Multiethnic Study of Breast Arterial Calcium Gradation and Cardiovascular Disease) demonstrated that presence of BAC conferred additional risk at every category (ie, low, medium, and high risk) of the pooled cohort equation.**17** While our study does not address CVD risk discrimination modeling, we demonstrate that BAC can reliably be

quantified using a novel AI algorithm and is independently associated with mortality and various CVD outcomes, which is a crucial and impactful step in this field. Future work will assess whether BAC scores can improve existing risk assessments for CVD outcomes, especially among women of intermediate ASCVD risk to guide initiation of preventive measures, such as statins, similar to CAC scores as suggested in the 2018 American College of Cardiology/American Heart Association Cholesterol Guidelines.**23** Ultimately, BAC scores may offer important and personalized risk stratification information, especially for younger women, without additional time, cost, and radiation.**24**

Study limitations

First, the retrospective nature of the study does not prove causality. Although attempts at reducing confounding factors using multivariable models were used, residual risk remains. Second, clinical data including outcomes relied on the use of ICD-10 codes from EHR data extraction, which introduces the possibility of misclassification. Also, mortality information only included all-cause mortality, but data on cause-specific mortality including CVD-related death were not available. Third, although EHRs allow for large aggregation of data and study populations with ICD codes for outcome ascertainment, misclassification still occurs. Additionally, while EHRs are becoming increasingly connected across hospital systems, follow-up information is still lost, especially among those who received care in other health systems. Fourth, follow-up varied for women in the study due to use of a strict censoring date, loss to follow-up, and development of events. However, regarding the composite outcome, there were only 146 women with <1 year of follow-up, and by the ninth year, there were still 9,804 women with follow-up data available (out of the 16,638 assessed for loss to follow-up; 17,720 total eligible for the composite outcome analyses and 1,082 developed events). Fifth, data on menopausal status were not available. Sixth, most subjects in this study identified as White, making results most applicable to this population. Seventh, our study design adjusted for history of several cardiovascular conditions based on ICD codes,

including history of MI, CAD, HF, and PAD. However, we do not have available information on specific CV interventions, such as PCI, coronary artery bypass graft, or valve replacements. Lastly, this study shows the characteristics and outcomes from a single-center, albeit with a large cohort of women. Our ongoing work focuses on assessing the implications of BAC across more diverse populations to increase external validity of this potential screening tool and to identify additional areas to improve risk assessment.

Conclusions

In this large, retrospective study, both BAC presence and quantity are significantly and independently associated with mortality and CVD outcomes. BAC appears to be especially predictive of CVD risk among younger women. Reporting of BAC was feasible and reliable using an automated AI algorithm, which could facilitate reporting uptake within the radiology community. Further studies are needed to determine the appropriate clinical response to BAC, and whether such a response can improve CVD outcomes in women.

5. Incidence of Congenital Heart Defects in Children Born After Assisted Reproductive Technology

It is estimated that more than 10 million children have been conceived through assisted reproductive technology (ART), and health outcomes for children born after ART are of great interest. Low birth weight and preterm birth have been found to be associated with birth defects in children conceived through ART.

In a population-based study involving 7.7 million liveborn children from four Nordic countries (Denmark, Finland, Norway, and Sweden), Sargisian and colleagues reported a higher risk of congenital heart defects (CHDs) in children born through ART than in those spontaneously conceived (aOR, 1.36; 95% CI, 1.31–1.41).1 Multi-fetal pregnancies were associated with the highest risk of CHD, regardless of the conception method. There were no differences in the incidence of CHD between children conceived through in

vitro fertilization and those conceived through intracytoplasmic sperm injection. These findings support the recommendation by the American Heart Association that fetal echocardiography is recommended for pregnancies conceived through ART.2

6. Sex-specific prediction of cardiogenic shock after acute coronary syndromes: the SEX-SHOCK score

Introduction

Acute coronary syndrome (ACS) continues to cause high morbidity and mortality across the globe. Of all patients presenting with ACS, 2%–10% develop cardiogenic shock (CS).1 Despite the tremendous progress made in stabilized patients with ACS, mortality rates of CS plateaued at ~ 50% 1 year after the index event.2–4 The survival benefit conferred by mechanical circulatory support (MCS) remains controversial,5,6 with international guidelines unequivocally supporting immediate revascularization of the infarct-related artery as the primary strategy to reduce CS-related mortality (class I recommendation).7,8

The Society for Cardiovascular Angiography and Interventions (SCAI) proposed a three-axis model to risk stratify patients across the CS continuum, with increasing stages associating with higher mortality risk.9 While SCAI stage B is considered as the pre-shock phase, stage C is hallmarked by the presence of organ hypoperfusion with a dismal prognosis and very limited therapeutic options.5,9 Assessing CS risk before hypoperfusion sets in may allow the implementation of therapeutic measures to prevent its progression to overt CS. This may represent a completely novel avenue to improve the management and outcomes of patients at high risk for the development of CS.

The Observatoire Régional Breton sur l'Infarctus (ORBI) score is the first risk score for the identification of ACS patients undergoing percutaneous coronary intervention (PCI) at risk of developing CS during hospital stay,

thus enabling effective risk stratification according to individual susceptibilities for CS as a basis for contemporary management and future interventional trials.10 However, ORBI was developed in a predominantly male patient population and marked differences in ACS pathobiology between females and males may have insufficiently been accounted for.11 Indeed, compared to their male counterparts, female ACS patients are older, have a higher comorbidity burden, experience longer pre-hospital delays, and are less likely to receive early revascularization or to be referred to tertiary-care shock centres, which is collectively linked to higher mortality risk.12–15

In this large multinational study, we aimed (i) to assess the sex-specific performance of ORBI in predicting in-hospital CS in patients with ACS, and (ii) to develop a refined model on sex-disaggregated data to achieve refined risk prediction across the entire spectrum of ACS in females and males.

Methods

Study design and outcome definition

This is a retrospective analysis of existing cohort studies. In Switzerland, patient data were retrieved from two independent cohorts, namely the Acute Myocardial Infarction in Switzerland Plus (AMIS-Plus) study16,17 and the Special Programme University Medicine Acute Coronary Syndrome (SPUM-ACS) study.18–21 AMIS-Plus is a nationwide cohort study comprising 46 939 patients with ACS (recruitment period: 1 January 2005 until 27 August 2020), of which 35 650 underwent PCI. The SPUM-ACS study is an investigator-initiated prospective cohort study comprising a total of 4787 ACS patients presenting to any of the four major university hospitals in Switzerland (recruitment period: 8 December 2009 until 31 December 2017), of which 4186 underwent PCI. In France, patient data were retrieved from the obseRvatoire des Infarctus de Côte-d'Or (RICO) study which comprises 21 229 ACS patients recruited between 2001 and 2022,22 with 13 701 undergoing PCI. The study protocols of each cohort were approved by the

local ethics committees and all study participants provided written informed consent. The primary endpoint was the occurrence of CS during initial hospitalization. Given the unavailability of (invasive) haemodynamic parameters and certain biomarkers in all-comers of patients with ACS, such as the cardiac index (<2.2 L/min/m2), pulmonary capillary wedge pressure (>15 mmHg), and lactate levels, in-hospital CS was defined as both a systolic blood pressure ≤ 90 mmHg after exclusion of hypovolaemia, and clinical signs of hypoperfusion, accompanied by the reliance on vasopressors/inotropic support or mechanical left ventricular assistance, as determined by treating physicians (see Supplementary data online, *Table S1*).10,23 Patients already presenting with overt CS on admission were excluded from the analysis (see Supplementary data online, *Figure S1*).

Evaluation of model performance

Model discrimination was assessed separately for female and male patients using the area under the receiver operating characteristic (ROC) curve (AUC) and compared using the DeLong test for unpaired ROC curves. Model calibration was evaluated by the Brier score and calibration plots (see Supplementary data online, *Figure S2*). For the assessment of overall model performance, we computed the accuracy, false omission rate, sensitivity, specificity, positive predictive value, negative predictive value, and the F1 score.24,25 To compare risk reclassification between SEX-SHOCK and ORBI, the integrated discrimination improvement and continuous net reclassification improvement were calculated. Decision curve analysis was conducted to compare the net benefit of the two models across different decision thresholds for predicting in-hospital CS.26

Development and validation of SEX-SHOCK

Variable selection

A whole panel of variables, including clinical, biochemical, electrocardiographic, and imaging-derived variables, was selected based on clinical plausibility and data availability (see Supplementary

data online, *Table S2*).27,28 Predictive models were then built using logistic regression (LR) and machine-learning models, i.e. random forest (RF) and multilayer perceptron (MLP). Feature importance was assessed using tailored methods for each model. In LR models, Wald x2 minus degrees of freedom was used.19 In RF models, the Gini index served as the performance measure,29 while for MLP, the permutation feature importance method was used, a proxy of the impact on model performance when features are shuffled.30

Model selection and validation

Forward selection and backward elimination methods were employed in a sex-specific fashion to identify the optimal variable combination with the lowest Akaike Information Criteria.25,31 The derivation cohort (AMIS-Plus) was randomly split into a training set (80% patients) and an internal testing set (20% patients). The training set was used to train RF, MLP, and LR models. Meanwhile, the internal testing set was utilized to assess their performance on unseen data and refine their hyperparameters. Following variable selection, LR and machine-learning-based models were compared to determine the best-performing modelling approach. Multicollinearity within the final model was assessed by the variance inflation factor and tolerance (see Supplementary data online, *Table S3*). Finally, SEX-SHOCK was internally validated using 10-fold cross-validation,32 with external validation being done in RICO (France) and SPUM-ACS (Switzerland).

Statistical analysis

Continuous variables are shown as median and interquartile range (IQR), while categorical data are presented as counts and valid percentages. Continuous variables were compared using Student's *t*-test or Mann–Whitney test if non-normally distributed, and categorical data were analysed using x2, Fisher's exact, or Kruskal–Wallis test, as appropriate. The degree of missing data is detailed in Supplementary data online, *Table S4* (see Supplementary data online). To mitigate a potential missing data

bias, multiple imputation using chained equations (MICE; n = 20 imputations) was performed for each cohort and sex separately. We employed predictive mean matching for continuous variables, proportional odds models for ordinal variables, and LR for binary variables, with in-hospital CS serving as the outcome variable.33,34 Receiver operating characteristic curves and calibration plots were generated using a randomly selected dataset from the multiply imputed datasets. Finally, nomograms were constructed separately for each sex by converting the regression coefficients of multivariable-adjusted regression models proportionally to a 0–100-point scale. Total-point scores were obtained by summing the points assigned to each variable. Findings are reported in accordance with the guidelines set forth in the TRIPOD statement (see Supplementary data online, *Figure S3*) for transparent prediction model reporting and align with the standards of the STROBE initiative (see Supplementary data online, *Figure S4*). If not stated otherwise, a $P < .05$ was deemed significant. All analyses were performed in R (version 4.1.2) and IBM SPSS (version 27.0.1). Additional details on the variable and model selection process are provided in the Supplementary data online.

Results

Patients

A total of 35 650 ACS patients were included in AMIS-Plus, of which 8481 were female (24.80%). Female patients exhibited marked differences in baseline characteristics, ORBI components (*Table 1*), and ACS management as compared to males (see Supplementary data online, *Table S5*). They were older than males (median age: 71.5 [61.5, 79.3] vs. 62.5 [54.0, 72.1] years; $P < .001$) and the prevalence of previous stroke or transient ischaemic attack was higher (5.4% vs. 4.0%; $P < .001$). Additionally, females experienced longer pre-hospital delays relative to males (median: 420.0 [201.0, 1200.0] vs. 350.0 [172.0, 1012.0] min; $P < .001$). Females also tended to present with higher Killip classes ($P < .001$), although their systolic blood pressure levels were slightly higher (138.0 [120.0, 158.0] vs.

135.0 [120.0, 155.0]; *P* < .001). Blood glucose levels (median: 7.4 [6.2, 9.3] vs. 7.1 [6.1, 8.8] mmol/L; *P* < .001), and heart rates (median: 76.0 [66.0, 88.0] vs. 75.0 [65.0, 87.0] min−1; *P* < .001) of female patients were also higher, suggesting an accentuated sympathetic response.

Table 1

Baseline characteristics of all patients stratified by sex in the nationwide AMIS-Plus study

	All patients (*N* = 35 650)	**Females (*N* = 8481)**	**Males (*N* = 27 169)**	***P* value**
ORBI components				
Age	64.5 [55.2, 74.4]	71.5 [61.5, 79.3]	62.5 [54.0, 72.1]	<.001
Presentation as cardiac arrest	1455 (4.1)	284 (3.3)	1171 (4.3)	<.001
Previous stroke/TIA	1529 (4.4)	451 (5.4)	1078 (4.0)	<.001
Anterior myocardial infarction	12 828 (36.5)	3077 (36.7)	9751 (36.4)	.566
First medical contact-to-PCI delay, min	365.0 [178.0, 1055.0]	420.0 [201.0, 1200.0]	350.0 [172.0, 1012.0]	<.001
Killip				<.001

	All patients (*N* = 35 650)	**Females (*N* = 8481)**	**Males (*N* = 27 169)**	***P* value**
I	32 190 (90.3)	7410 (87.4)	24 780 (91.2)	
II	2503 (7.0)	759 (8.9)	1744 (6.4)	
III	689 (1.9)	236 (2.8)	453 (1.7)	
Heart rate, min−1	75.0 [65.0, 87.0]	76.0 [66.0, 88.0]	75.0 [65.0, 87.0]	<.001
Systolic blood pressure, mmHg	136.0 [120.0, 155.0]	138.0 [120.0, 158.0]	135.0 [120.0, 155.0]	<.001
Pulse pressure, mmHg	55.0 [43.0, 70.0]	60.0 [46.0, 75.0]	54.0 [42.0, 67.0]	<.001
Glucose, mmol/L	7.1 [6.1, 8.9]	7.4 [6.2, 9.3]	7.1 [6.1, 8.8]	<.001
TIMI flow post-PCI				.109
0	318 (1.3)	84 (1.4)	234 (1.2)	

	All patients (*N* = 35 650)	**Females (*N* = 8481)**	**Males (*N* = 27 169)**	***P* value**
I	217 (0.9)	62 (1.1)	155 (0.8)	
II	1057 (4.2)	258 (4.4)	799 (4.2)	
III	23 345 (93.6)	5409 (93.1)	17 936 (93.8)	
Candidate predictors				
C-reactive protein, mg/L	4.0 [2.0, 9.0]	5.0 [2.0, 11.0]	4.0 [2.0, 9.0]	<.001
Creatinine, μmol/L	82.0 [70.0, 97.0]	72.0 [61.0, 87.0]	85.0 [74.0, 99.0]	<.001
ST-segment elevation	20 743 (58.2)	4877 (57.5)	15 866 (58.4)	.143
Left ventricular ejection fraction				.048
<35%	1777 (7.4)	462 (8.1)	1315 (7.2)	
35%–50%	8607 (35.8)	2046 (36.0)	6561 (35.8)	

	All patients (*N* = 35 650)	**Females (*N* = 8481)**	**Males (*N* = 27 169)**	***P* value**
>50%	13 626 (56.8)	3183 (55.9)	10 443 (57.0)	
SCAI class				
Aa	29 690 (85.6)	6824 (82.8)	22 866 (86.5)	<.001
Bb	5960 (16.7)	1657 (19.5)	4303 (15.8)	<.001
Biochemical and haemodynamic parameters				
NT-proBNP, ng/L	898.0 [230.0, 2540.5]	1480.0 [459.0, 4333.5]	745.5 [191.0, 2117.0]	<.001
White blood cells, /µL	9800.0 [7800.0, 12 400.0]	9770.0 [7800.0, 12 300.0]	9810.0 [7800.0, 12 400.0]	.08
HbA1c, %	5.7 [5.4, 6.1]	5.7 [5.4, 6.1]	5.7 [5.4, 6.1]	.912
Haemoglobin, g/dL	14.4 [13.2,	13.2 [12.2,	14.7 [13.7,	<.001

	All patients (*N* = 35 650)	**Females (*N* = 8481)**	**Males (*N* = 27 169)**	***P* value**
	15.4]	14.2]	15.7]	
eGFR, mL/min/1.73 m2	81.6 [65.1, 94.5]	73.9 [56.7, 88.7]	83.8 [68.1, 95.9]	<.001
Diastolic blood pressure, mmHg	80.0 [70.0, 90.0]	78.0 [67.0, 88.0]	80.0 [70.0, 91.0]	<.001
Medical history				
FHx of CAD (first degree relatives < 60 years)	10 146 (34.4)	2491 (36.2)	7655 (33.8)	<.001
Previous stable angina	5493 (15.7)	1244 (15.0)	4249 (15.9)	.038
Previous myocardial infarction	5300 (15.1)	983 (11.8)	4317 (16.2)	<.001
Previous PCI	5789 (16.5)	1072 (12.9)	4717 (17.7)	<.001
Previous CABG	1623 (4.6)	275 (3.3)	1348 (5.0)	<.001
Hypertension	20 770 (61.3)	5599 (69.0)	15 171 (58.8)	<.001

	All patients (*N* = 35 650)	**Females (*N* = 8481)**	**Males (*N* = 27 169)**	***P* value**
Diabetes	6476 (19.0)	1735 (21.5)	4741 (18.2)	<.001
Hypercholesterolaemia	20 337 (63.2)	4636 (61.1)	15 701 (63.8)	<.001
Comorbidities				
Malignancy	1325 (3.8)	332 (4.0)	993 (3.7)	.274
Peripheral arterial diseases	1429 (4.1)	394 (4.7)	1035 (3.9)	.001
Hemiplegia	120 (0.3)	31 (0.4)	89 (0.3)	.67
Dementia	315 (0.9)	143 (1.7)	172 (0.6)	<.001
Chronic lung disease	1708 (4.9)	437 (5.3)	1271 (4.8)	.074
Connective tissue disease	426 (1.2)	204 (2.5)	222 (0.8)	<.001
Peptic ulcer disease	501 (1.4)	145 (1.7)	356 (1.3)	.007
Moderate to severe liver disease	166 (0.5)	35 (0.4)	131 (0.5)	.47

	All patients (*N* = 35 650)	**Females (*N* = 8481)**	**Males (*N* = 27 169)**	***P* value**
Moderate to severe renal disease	1840 (5.3)	568 (6.8)	1272 (4.8)	<.001
ECG on admission				
Q-waves	2142 (6.0)	440 (5.2)	1702 (6.3)	<.001
ST-segment depression	8549 (24.0)	2210 (26.1)	6339 (23.3)	<.001
T-wave changes	6592 (18.5)	1759 (20.7)	4833 (17.8)	<.001
Left bundle branch block	890 (2.5)	249 (2.9)	641 (2.4)	.003
Right bundle branch block	1104 (3.1)	180 (2.1)	924 (3.4)	<.001
Type of vessel disease				
1-VD	14 152 (40.1)	3576 (42.6)	10 576 (39.3)	<.001
2-VD	10 923 (30.9)	2548 (30.3)	8375 (31.1)	.183
3-VD	9929 (28.1)	2171 (25.8)	7758 (28.8)	<.001

	All patients (*N* = 35 650)	**Females (*N* = 8481)**	**Males (*N* = 27 169)**	***P* value**
LMCAD	592 (1.7)	135 (1.6)	457 (1.7)	.607
Culprit vessel				<.001
Left main	431 (2.1)	85 (1.8)	346 (2.3)	
Left anterior descending artery (or one of its branches)	8448 (42.1)	2004 (41.8)	6444 (42.2)	
Left circumflex artery (or one of its branches)	3737 (18.6)	828 (17.3)	2909 (19.0)	
Right coronary artery (or one of its branches)	6937 (34.6)	1774 (37.0)	5163 (33.8)	
Other	437 (2.2)	84 (1.8)	353 (2.3)	
Type of MIc				<.001
Type 1	21 758 (92.3)	5204 (92.4)	16 554 (92.2)	
Type 2	934 (4.0)	265 (4.7)	669 (3.7)	
Type 3	11 (0.0)	5 (0.1)	6 (0.0)	

	All patients (*N* = 35 650)	**Females (*N* = 8481)**	**Males (*N* = 27 169)**	***P* value**
Type 4a	81 (0.3)	17 (0.3)	64 (0.4)	
Type 4b	724 (3.1)	129 (2.3)	595 (3.3)	
Type 5	66 (0.3)	9 (0.2)	57 (0.3)	
Location of MI				
Inferior	13 152 (37.4)	3179 (38.0)	9973 (37.2)	.225
Posterior	3432 (9.8)	806 (9.7)	2626 (9.8)	.674
Lateral	3849 (15.7)	979 (16.7)	2870 (15.4)	.018
TIMI flow of culprit vessel pre-PCI				.239
0	7601 (54.6)	1763 (53.2)	5838 (55.0)	
I	2861 (20.5)	719 (21.7)	2142 (20.2)	
II	1546 (11.1)	360 (10.9)	1186 (11.2)	
III	1925	473	1452	

	All patients (*N* = 35 650)	Females (*N* = 8481)	Males (*N* = 27 169)	*P* value
	(13.8)	(14.3)	(13.7)	
PCI complications				
Myocardial infarction after PCI	140 (0.6)	34 (0.6)	106 (0.6)	.996
Emergency CABG after PCI	20 (0.1)	7 (0.1)	13 (0.1)	.368
Pericardiocentesis	42 (0.2)	18 (0.3)	24 (0.1)	.007
Intraprocedural death	64 (0.3)	28 (0.5)	36 (0.2)	<.001

Data are shown as median [IQR] or N (valid %).

CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate, calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation; FHx of CAD, family history of coronary artery disease; HbA1c, haemoglobin A1c; LMCAD, left main coronary artery disease; NT-proBNP, N-terminal pro b-type natriuretic peptide; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; TIMI, thrombolysis in myocardial infarction; 1/2/3 VD, 1/2/3 vessel disease.

aDefined as warm and well-perfused with normal JVP (Killip I) and SBP ≥ 100 mmHg.

bDefined as having elevated JVP (Killip II or higher), SBP < 90 mmHg, and/or no signs of classic CS (Killip IV).9

cDefined according to the fourth universal definition of acute myocardial infarction.

Female patients were more likely to have impaired systolic function, as defined by left ventricular ejection fraction (LVEF) < 35%, as compared to their male counterparts (8.1% vs. 7.2%; *P* = .048). Women also had higher C-reactive protein (CRP) levels than males (median: 5.0 [2.0, 11.0] vs. 4.0 [2.0, 9.0] mg/L; *P* < .001), suggesting a greater inflammatory burden at the time of acute presentation. Despite lower creatinine levels among females, their estimated glomerular filtration rate (eGFR), a sex-adjusted measure of renal function, implied more severe renal impairment. In AMIS-Plus, 3.1% of all patients experienced in-hospital CS, with a higher relative incidence among females as compared to males (3.9% vs. 2.8%; *P* < .001). Sex-specific differences in baseline and management characteristics were similarly observed in RICO, in which a total of 13 701 patients were included. In these patients, 5.3% and 3.7% of female and male patients, respectively, developed in-hospital CS (*P* < .001) (see Supplementary data online, *Tables S6* and *S7*).

Sex-specific performance of ORBI

While ORBI provided good discriminatory performance for the prediction of in-hospital CS in males (AUC [95% CI]: 0.81 [0.79–0.83]), its performance was lower in female patients recruited in Switzerland (0.78 [0.76–0.81]; *P* = .048) (*Figure 1A*). Similar results were obtained in French patients (males: 0.84 [0.81–0.86] vs. females: 0.77 [0.74–0.81]; *P* = .002) (*Figure 1B*). Indeed, in both Switzerland and France, ORBI performance among female ACS patients was characterized by higher Brier scores (i.e. a measure of prediction accuracy) and false omission rates (i.e. proportion of false negatives) as compared to males (see Supplementary data online, *Table S8*). Collectively, these findings indicate a limited sex-specific performance, with the ORBI risk score being more likely to miss true positives in females, thus systematically underestimating in-hospital CS risk in women.

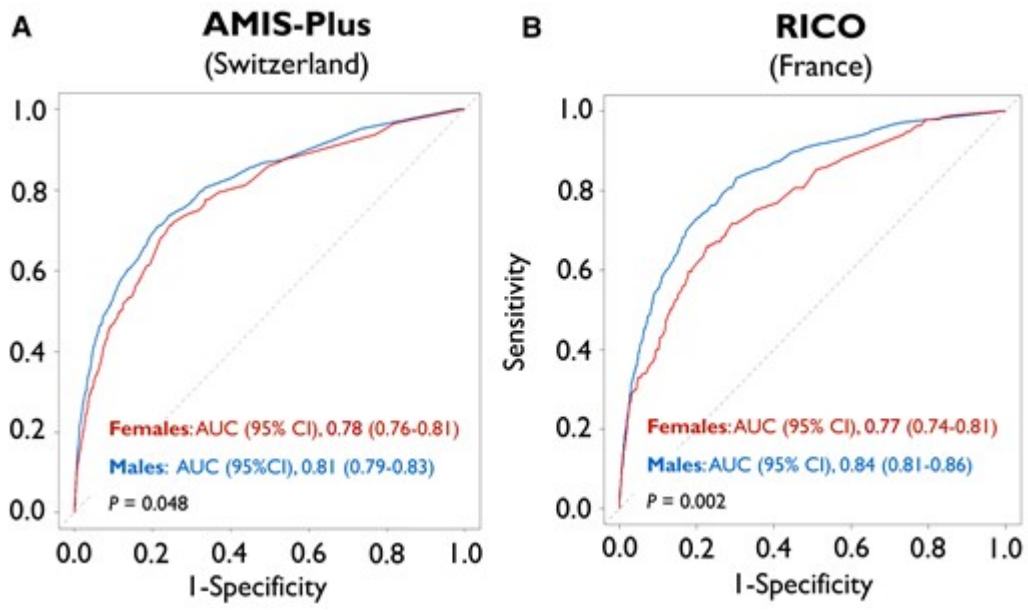

Figure 1

Sex differences in ORBI performance in ACS patients undergoing PCI in Switzerland (left) and France (right). ROC curves of the ORBI risk score for the prediction of in-hospital cardiogenic shock are shown for female (red) and male patients (blue) in (*A*) AMIS-Plus (Switzerland) and (*B*) RICO (France). ROC curves were compared using an unpaired DeLong test. AMIS-Plus, Acute Myocardial Infarction in Switzerland Plus; AUC, area under the ROC curve; CI, confidence interval; ORBI, Observatoire Régional Breton sur l'Infarctus; PCI, percutanous coronary intervention; RICO, obseRvatoire des Infarctus de Côte-d'Or; ROC, receiver operating characteristic

Development of SEX-SHOCK

To address these limitations and consider sex-specific disease characteristics, we used machine-learning algorithms (i.e. RF and MLP) and LR on sex-disaggregated data and ranked potential predictors by feature importance separately for females and males (see Supplementary data online, *Figure S5*). The top 10 variables in females and males are depicted in *Figure 2A–C*. For females, top 10 variables across all modelling tactics tested included creatinine, CRP, LVEF, ST-segment elevation, and diabetes, while in males, CRP, LVEF, ST-segment elevation, and a history of dyslipidaemias provided marked predictive value towards incident CS.

Finally, overlapping features (i.e. creatinine, CRP, LVEF, and ST-segment elevation) were selected as candidate variables to refine ORBI (*Figure 2D*, Supplementary data online, *Figure S6*). Forward selection and backward elimination were used to determine the optimal variable combination, with prior stroke/transient ischaemic attack, anterior ST-segment elevation myocardial infarction (STEMI), first medical contact-to-PCI delay, and Killip class II being replaced by creatinine, CRP, LVEF, and ST-segment elevation (see Supplementary data online, *Tables S9* and *S10*). Among all model building approaches tested, LR emerged as the preferred method (see Supplementary data online, *Figure S7*), demonstrating highest predictive accuracy for both sexes. By combining best-performing variables with top-performing models, SEX-SHOCK was developed (see Supplementary data online, *Figure S8*).

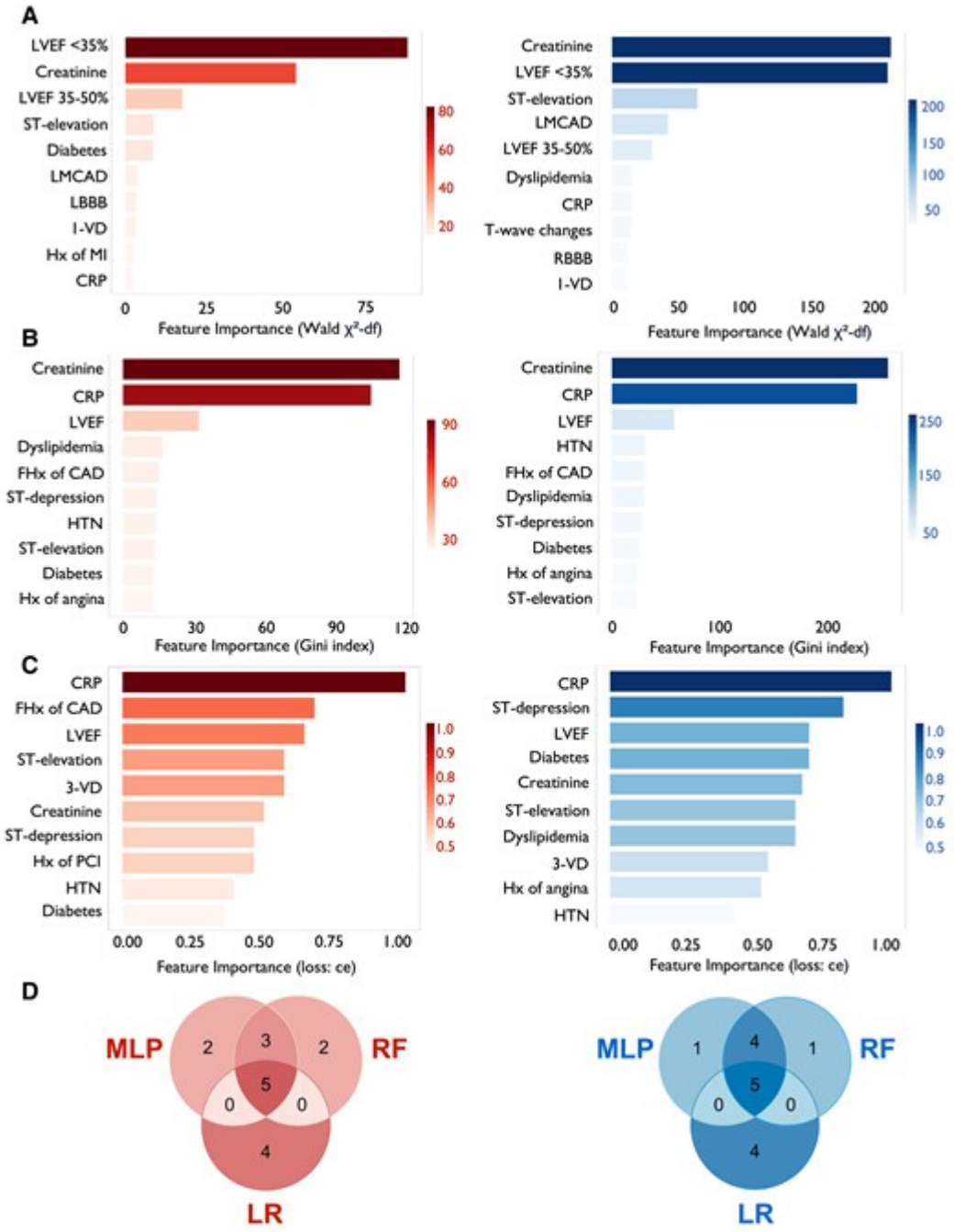

Figure 2

Identification of most important predictors of in-hospital cardiogenic shock depending on sex. Top 10 variables identified by (*A*) logistic regression (LR), (*B*) random forest (RF), and (*C*) multilayer perceptron (MLP) in females (left; red) and males (right; blue). (*D*) Venn plots showing the intersection of highest-ranked predictors identified by LR, RF, and MLP in females (left; red) and males (right; blue). For females, the five overlapping variables include CRP, ST-segment elevation, LVEF, creatinine, and diabetes. For males, CRP,

ST-segment elevation, history of dyslipidaemias, creatinine, and LVEF are among most important predictors across all model building approaches tested. LVEF was dummy coded in LR models. CAD, coronary artery disease; CRP, C-reactive protein; FHx, positive family history; HTN, history of hypertension; Hx, history of; LBBB, left bundle branch block; LMCAD, left main coronary artery disease; LVEF, left ventricular ejection fraction; MLP, multilayer perceptron; RBBB, right bundle branch block; RF, random forest; LR, logistic regression; 1-VD, single-vessel disease; 3-VD, three-vessel disease

Evaluation of SEX-SHOCK

Although relying on the identical number of predictors (n = 12), the discriminatory performance of SEX-SHOCK outperformed ORBI for the prediction of in-hospital CS in females (0.81 [0.78–0.83] vs. 0.78 [0.76–0.81], P < .001) and males alike (0.83 [0.82–0.85] vs. 0.81 [0.79–0.83], P < .001) (*Figure 3A* and *B*). SEX-SHOCK showed improved sensitivity, F1 score, false omission rate, and positive predictive value in both sexes (*Figure 3C* and *D*; Supplementary data online, *Table S11*). Decision curve analysis suggested that the net benefit of SEX-SHOCK at different decision thresholds surpassed that of ORBI in both sexes alike (*Figure 4*). Furthermore, irrespective of sex, SEX-SHOCK showed higher net reclassification and integrated discrimination improvement as compared to ORBI, emphasizing its superior performance as regards risk reclassification in both Swiss and French ACS patients (*Table 2*).

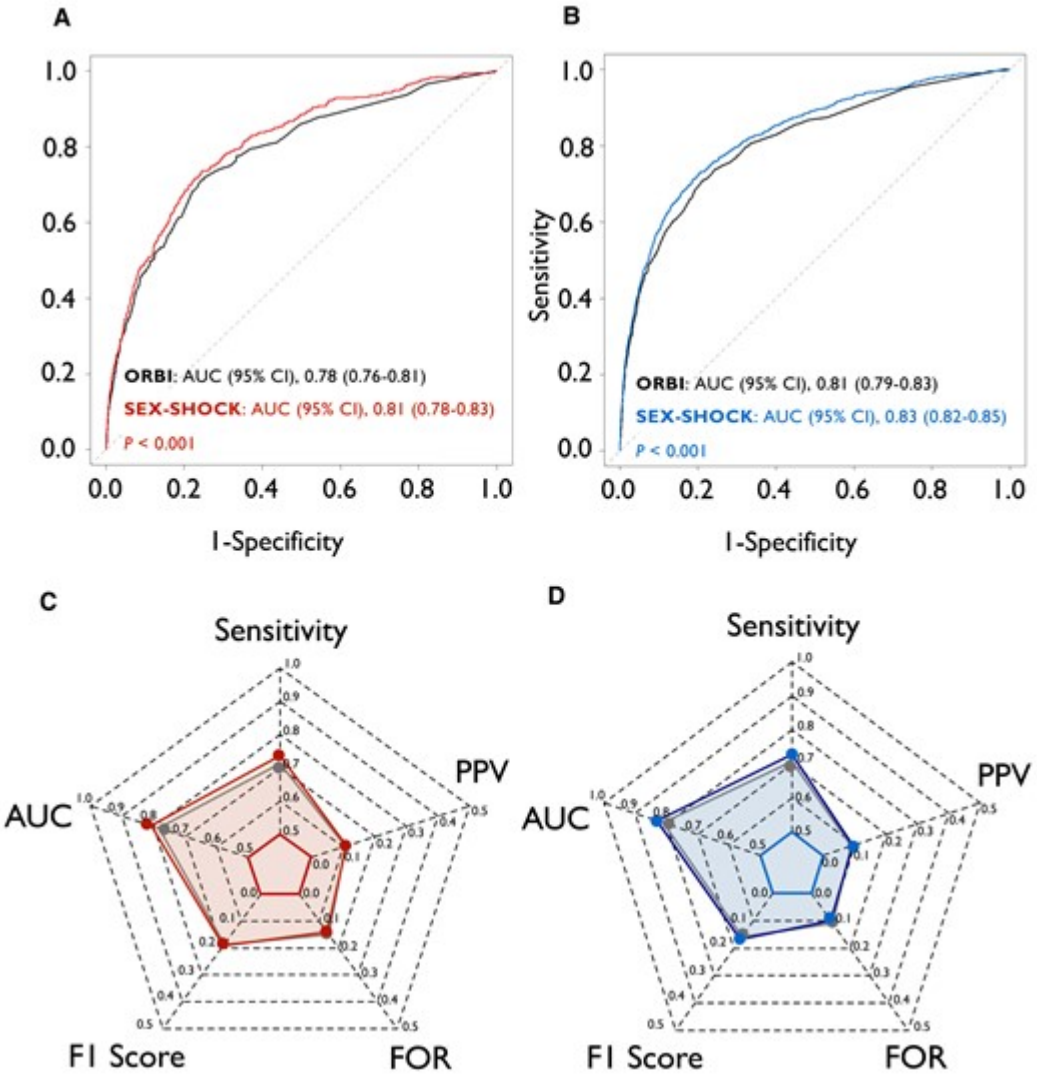

Figure 3

Performance of ORBI and SEX-SHOCK in the derivation cohort. ROC curves of the ORBI (black) and SEX-SHOCK score in (*A*) females (left; red) and (*B*) males (right; blue). ROC curves were compared using an unpaired DeLong test. Radar plots illustrate sensitivity, AUC, F1 score, false omission rate, and positive predictive value for the ORBI (grey area) and SEX-SHOCK score in (*C*) females (red area) and (*D*) males (blue area). AUC, area under the ROC curve; CI, confidence interval; FOR, false omission rate; ORBI, Observatoire Régional Breton sur l'Infarctus; PPV, positive predictive value; ROC receiver operating characteristic.

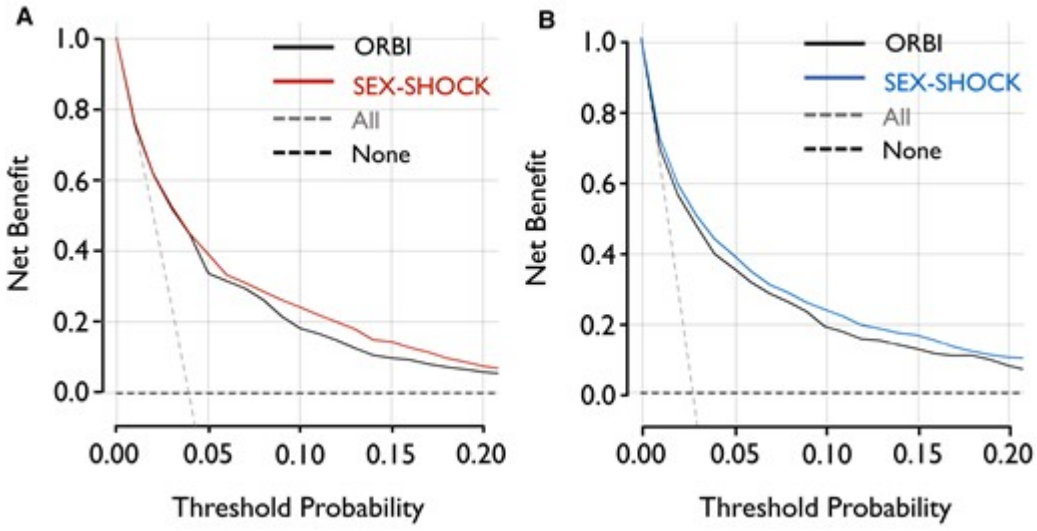

Figure 4

Sex-stratified decision curve analysis comparing the SEX-SHOCK vs. ORBI risk score. Net benefit of the ORBI (black) and SEX-SHOCK score in predicting in-hospital cardiogenic shock in (*A*) females (left; red) and (*B*) males (right; blue) assuming that all (dashed grey line) or none (dashed back line) patients are at high risk across different risk thresholds. ORBI, Observatoire Régional Breton sur l'Infarctus

Table 2

Reclassification value of SEX-SHOCK vs. ORBI

Cohort	**NRI (95% CI)**	***P* value**	**IDI (95% CI)**	***P* value**
Females				
AMIS-Plus	0.376 (0.267–0.484)	<.001	0.016 (0.009–0.024)	<.001
SPUM-ACS	0.485 (0.189–0.781)	.001	0.035 (0.003–0.068)	.031
RICO	0.500 (0.358–0.642)	<.001	0.033 (0.017–0.049)	<.001

Cohort	NRI (95% CI)	*P* value	IDI (95% CI)	*P* value
Males				
AMIS-Plus	0.323 (0.252–0.395)	<.001	0.016 (0.011–0.022)	<.001
SPUM-ACS	0.469 (0.313–0.625)	<.001	0.029 (0.013–0.044)	<.001
RICO	0.607 (0.507–0.706)	<.001	0.050 (0.037–0.063)	<.001

AMIS-Plus, Acute Myocardial Infarction in Switzerland Plus; CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification improvement; RICO, obseRvatoire des Infarctus de Côte-d'Or; SPUM-ACS, Special Programme University Medicine Acute Coronary Syndrome.

Internal and external validation of SEX-SHOCK

Following 10-fold cross-validation in AMIS-Plus (see Supplementary data online, *Figure S9*), the AUC for females ranged from 0.78 (95% CI, 0.67–0.89) to 0.91 (95% CI, 0.87–0.95), with a mean ± SD of 0.83 ± 0.05. In males, the AUC ranged from 0.82 (95% CI, 0.75–0.88) to 0.90 (95% CI, 0.85–0.94), with a mean ± SD of 0.86 ± 0.03. In both external validation cohorts (i.e. RICO and SPUM-ACS), SEX-SHOCK demonstrated superior discriminative performance as compared to ORBI (see Supplementary data online, *Figure S10*). Beyond the AUC, the sensitivity, the F1 score, and the positive predictive value were also improved, while false omission rate was reduced for both female and male patients (*Figure 5*, Supplementary data online, *Table S10*). Aligning with the data obtained in AMIS-Plus, decision curve analysis in both external validation cohorts suggested a greater net benefit of SEX-SHOCK in predicting in-hospital CS across various risk thresholds for both females and males (see Supplementary

data online, *Figure S11*). To enhance the clinical applicability of the SEX-SHOCK score and allowing score calculation prior to PCI, a simplified model was developed, solely relying on non-procedural variables, showing similar performance to the full model (see Supplementary data online, *Figure S12*), while retaining its superiority as compared to ORBI in both validation cohorts (see Supplementary data online, *Figure S13* and Supplementary data online, *Table S12*).

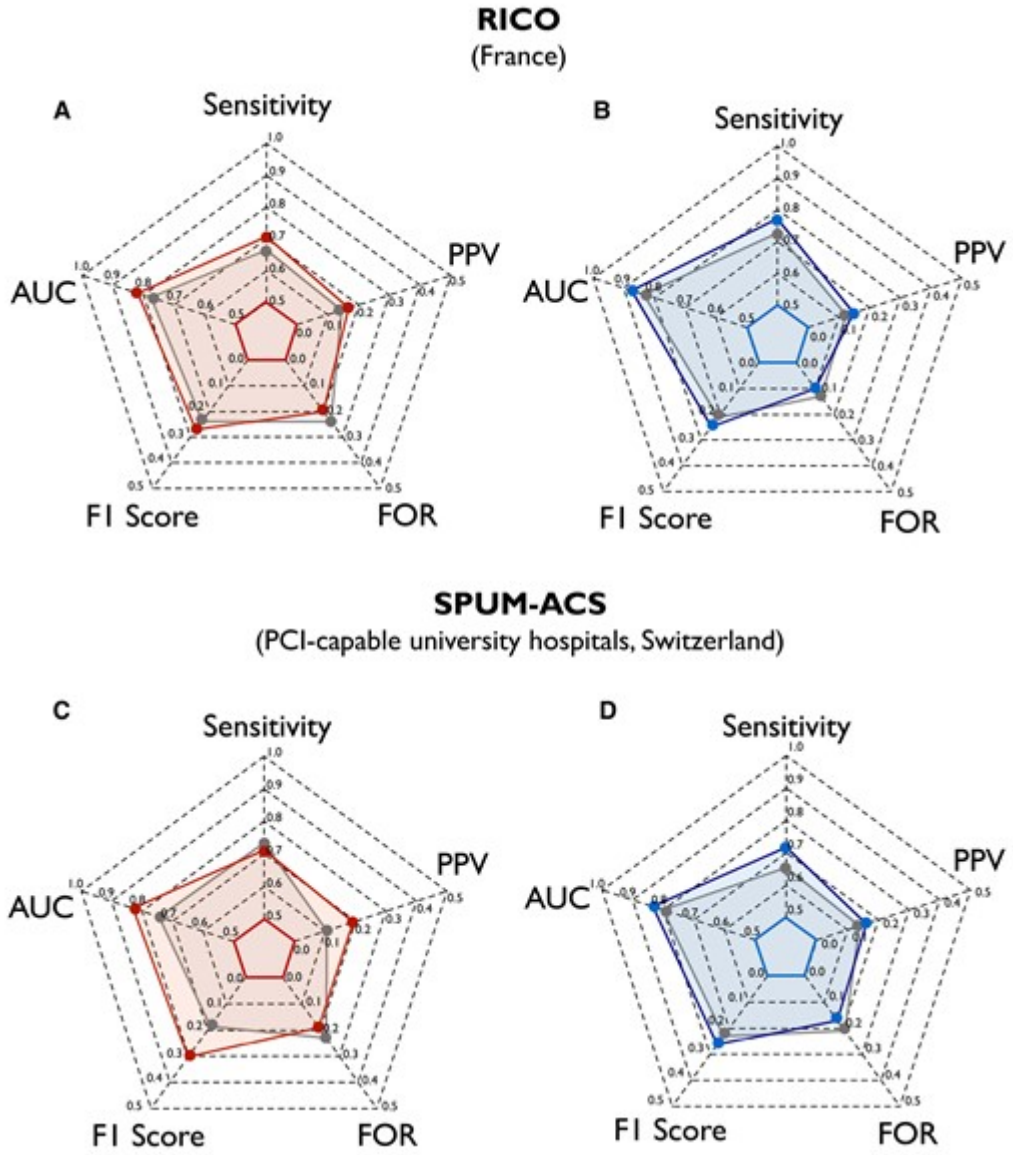

Figure 5

External validation of the newly developed SEX-SHOCK score. Radar plots showing the improved performance of the SEX-SHOCK score as compared to

ORBI in terms of sensitivity, AUC, F1 score, false omission rate, and positive predictive value for females (red area) and males (blue area) in RICO (*A, B*) and SPUM-ACS (*C, D*). AUC, area under the receiver operating characteristic curve; FOR, false omission rate; PPV, positive predictive value; RICO, obseRvatoire des Infarctus de Côte-d'Or; SPUM-ACS, Special Programme University Medicine Acute Coronary Syndrome.

Clinical application: nomogram of SEX-SHOCK

To allow for clinical use, sex-specific nomograms were developed for female and male ACS patients (*Figure 6*). Each predictor in SEX-SHOCK was assigned individual score points based on its individual contribution to overall CS risk. Individual score points were then summed to obtain a total score. Finally, using a function relating the total score to the probability of in-hospital CS, the predicted probability of in-hospital CS for each female or male ACS patient was calculated. Scores corresponding to different levels of each predictor used in the SEX-SHOCK model are detailed in Supplementary data online, *Table S13* (see Supplementary data online). The online calculator for clinical use is available via www.mdcalc.com/calc/10563/sex-shock-risk-score-development-cardiogenic-shock.

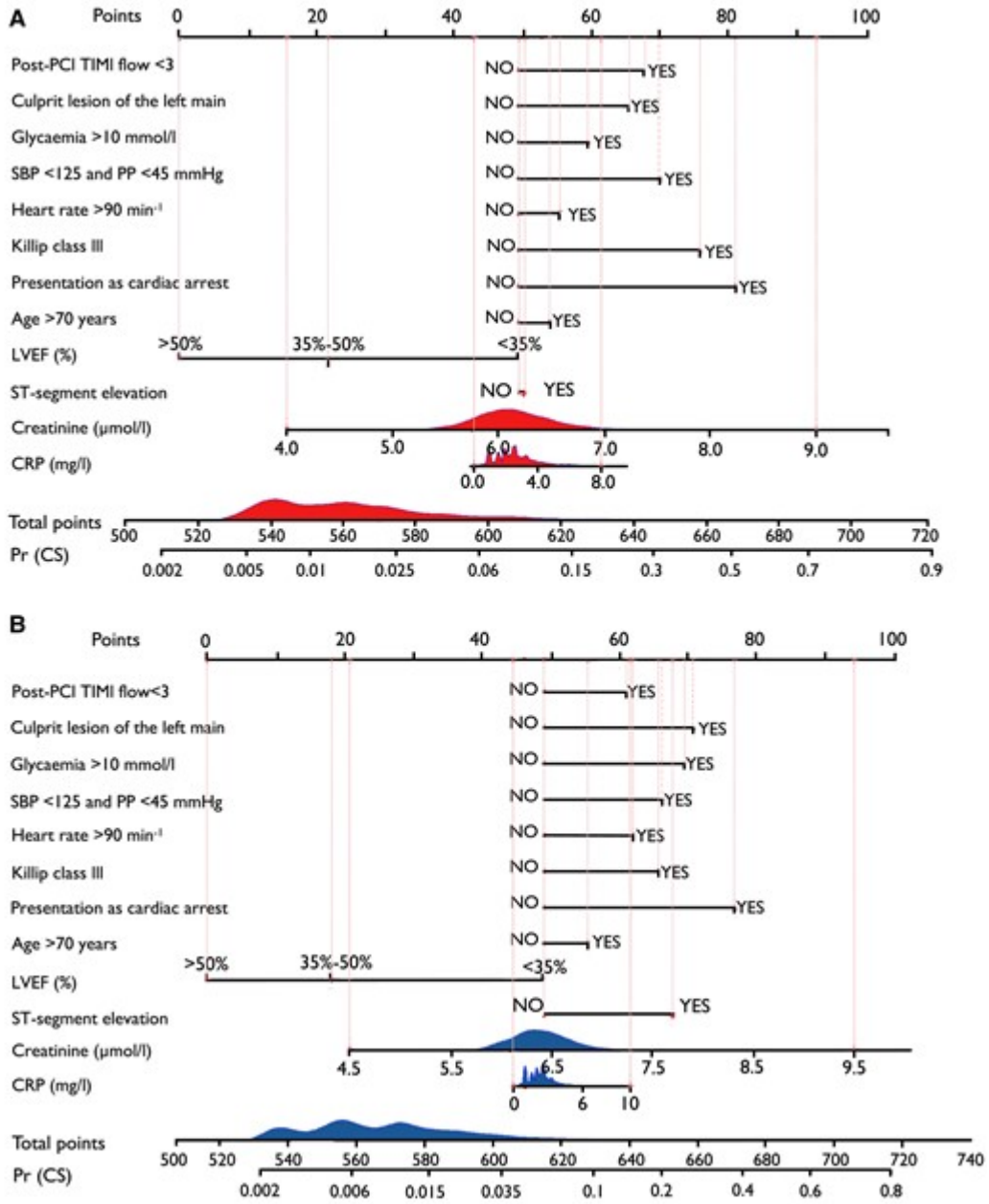

Figure 6

Nomogram for refined risk prediction of cardiogenic shock in acute coronary syndromes: the SEX-SHOCK score. Nomogram to calculate the probability of in-hospital cardiogenic shock in (*A*) female and (*B*) male patients. Points: assigned scores for each predictor level. Total points: sum of individual score points across all predictors. Predicted probability of cardiogenic shock [Pr (CS)] is calculated based on the total score and the conversion relationship between the probability of the outcome event. Score points assigned to each predictor are summarized in Supplementary data online, *Table S13* (see Supplementary data online). Given the skewed distribution of

biomarker data, CRP and creatinine values were log-transformed. LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; PP, pulse pressure; Pr (CS), predicted probability of cardiogenic shock; SBP, systolic blood pressure; TIMI, thrombolysis in myocardial infarction grade.

Discussion

Here, we demonstrate (i) that the ORBI risk score shows only modest performance in female ACS patients as compared to males, (ii) that CRP, LVEF, creatinine, and ST-segment elevation are potent predictors of in-hospital CS in both sexes, and (iii) that the newly developed SEX-SHOCK score, though relying on the identical number of variables, outperforms ORBI in both sexes across nations and clinical settings (*Structured Graphical Abstract*).

Currently available risk scores in the setting of CS, such as the IABP-SHOCK II,35 ENCOURAGE,36 SAVE,37 and CARD-SHOCK score,38 are primarily used to predict mortality and are applicable only to patients who present with, rather than being at risk of CS during hospitalization, thus serving solely as prognostic tools. Indeed, once ACS has progressed to overt CS (SCAI-C or higher), interventions tested so far might be implemented too late to change outcomes effectively. In fact, the efficacy and safety of mechanical or pharmacological support in reducing mortality in patients with established CS, despite one promising trial,39 remains highly controversial, and novel risk stratification strategies are urgently warranted.40–43 For instance, in both the DanGer SHOCK and ECLS-SHOCK trials, only patients with SCAI-C or higher were recruited, while patients with pre-hospital cardiac arrest were excluded from the former.39,43 Hence, to reduce overall mortality, it might be worth considering applying therapeutic strategies early (e.g. in those at high CS risk but not yet in SCAI-C) with the goal of preventing CS and its progression into a refractory stage, in which patients have a dismal prognosis. In contrast to previous studies, the herein included derivation and validation cohorts also comprised patients with pre-hospital cardiac

arrest and signs of myocardial ischaemia, with the SEX-SHOCK score being also applicable to these patients.

In daily clinical practice, patients in the pre-shock stage may be overlooked frequently due to the unavailability of quantifiable biomarkers for the differentiation between SCAI-A (at risk of CS) and SCAI-B (characterized by haemodynamic instability without organ hypoperfusion) and SCAI-C (organ hypoperfusion requiring pharmacologic or mechanical support).5 While soluble biomarkers of hypoperfusion, such as lactate, correlate well with short-term mortality in patients with overt CS,44 normal lactate levels do not exclude the presence of haemodynamic instability.45,46 By integrating clinical, biochemical, electrocardiographic, and imaging-derived features in a sex-specific fashion, SEX-SHOCK is the first internally and externally validated risk score to precisely estimate CS risk in the pre-shock phase in both females and males, potentially allowing timely identification of high-risk patients who may benefit from novel interventions to prevent the progression to overt CS.

For instance, LVEF, an important imaging parameter linked to adverse events in patients with CS, represents an important parameter to determine a patient's benefit from MCS and guiding treatment strategies to optimize expected benefits.47 Additionally, worsening renal function serves as an important proxy for end-organ hypoperfusion and has been incorporated into various CS scoring systems previously.35,36,48,49 Similarly, systemic inflammation plays a crucial role in CS pathobiology, contributing to its progression,50–52 with CS patients displaying higher levels of inflammatory markers [e.g. CRP, tumour necrosis factor α, and interleukin (IL)-6] as compared to controls, which may be linked to poor outcomes.51,53–55 Notably, anti-inflammatory therapy by IL-1β inhibition reduces total cardiovascular events in stabilized patients with prior ACS and high residual inflammatory burden,56,57 although the benefits of anti-inflammatory therapies for the prevention of CS development in ACS patients remains to be comprehensively investigated.

Of note, CS patients with non-ST-segment elevation ACS (NSTE-ACS) have a higher baseline risk profile than those with STEMI, with CS complicating NSTE-ACS typically occurring after a median of 76–94 h.58,59 Despite this, NSTE-ACS patients, whether they have established CS or not, undergo coronary angiography less frequently compared to STEMI patients, particularly if they are female.58,60 Moreover, although women present with NSTE-ACS more often, they receive timely guideline-recommended care less frequently as compared to males.61

Hence, objective risk assessment is particularly important for the management of female ACS patients, as these patients are older, have higher comorbidity burden, experience longer pre-hospital delays, are less likely to be referred to tertiary-care shock centres, and to receive early revascularization,15,62 making an optimal approach to a personalized treatment strategy challenging. The novel SEX-SHOCK score was trained and validated on sex-disaggregated data, provides objective risk assessment, and thus may mitigate sex inequities in the acute management of patients across the entire spectrum of ACS.

Strengths and limitations

Our study has several strengths. First, we analysed one of the largest and best characterized patient cohorts on ACS and CS in Europe, with a total sample size exceeding most previous studies on risk prediction in CS. Second, patients enrolled between 2005 and 2022 were analysed, accounting for the evolution of both ACS and CS phenotypes and thus reflecting evolving strategies of contemporary ACS management. Third, we used two different external validation cohorts, allowing to test the performance of SEX-SHOCK across healthcare systems, nations, and clinical settings.

Despite these strengths, certain limitations warrant discussion. First, the sex-specific differences in ORBI score performance were only modest in magnitude in AMIS-Plus. Second, although the superior performance of

SEX-SHOCK in both validation cohorts argues for a high predictive utility of CRP, data on this biomarker were only available in 67.6% of patients in derivation cohort. Additionally, data on initial lactate levels were unavailable in the derivation and validation cohorts; thus, future studies should assess whether the integration of biomarker data beyond CRP and creatinine can further improve SEX-SHOCK score performance.46 Along similar lines, given the unavailability of patients' ethnicity in the derivation cohort, additional studies might be warranted to assess the generalizability of the herein reported results across social–cultural aspects. Third, we did not assess the predictive performance of SEX-SHOCK over time (from study inclusion to discharge) due to unavailability of data on the exact time point of in-hospital CS. Indeed, the latter represents a major limitation of the present study, as certain patients may have moved to a higher SCAI class before all variables informing SEX-SHOCK were available. Fourth, as certain patients (e.g. those with pre-hospital cardiac arrest or those presenting in SCAI-B) might be underrepresented in the present study, independent validation studies are certainly warranted to probe score performance across patient subgroups and CS entities. Fifth, whether the clinically relevant improvements in risk prediction of SEX-SHOCK reflect into improved outcomes of ACS patients at risk of developing CS needs to be demonstrated in well-designed interventional trials. Finally, our study has certain limitations inherent to its observational design, including residual confounding. However, we would argue that our study results could inform the design of future interventional trials, focusing on a patient population at risk of rather than fully established CS.

Conclusions

By integrating best-performing models with highest-ranked predictors, the SEX-SHOCK score demonstrates excellent discriminatory performance for the prediction of in-hospital CS in both females and males across the entire spectrum of ACS, thus mitigating sex inequities in early risk stratification of contemporary ACS management. The SEX-SHOCK score facilitates the early

identification of ACS patients at high risk of CS and may guide contemporary clinical decision-making and patient selection for future randomized controlled trials.

7. Ischaemic heart disease: focus on sex-related differences and novel therapeutic targets

This focus issue on ischaemic heart disease and acute cardiovascular care contains the Fast Track Clinical Research article 'Sex-specific prediction of cardiogenic shock after acute coronary syndromes: the SEX-SHOCK score' by Yifan Wang from the University of Zurich in Switzerland, and colleagues.1 The authors point out that cardiogenic shock (CS) remains the primary cause of in-hospital death after acute coronary syndromes (ACS), with mortality rates approaching 50%.2–6 To test novel interventions, personalized risk prediction is essential. The ORBI (Observatoire Régional Breton sur l'Infarctus) score represents the first-of-its-kind risk score to predict in-hospital CS in ACS patients undergoing percutaneous coronary intervention (PCI). However, its sex-specific performance remains unknown, and refined risk prediction strategies are warranted. This multinational study included >53 000 ACS patients without CS on admission undergoing percutaneous coronary intervention. Following sex-specific evaluation of ORBI, regression and machine-learning models were used for variable selection and risk prediction. By combining best-performing models with highest-ranked predictors, SEX-SHOCK was developed, and internally and externally validated. The ORBI score showed lower discriminative performance for the prediction of CS in females than in males in Swiss (area under the receiver operating characteristic [AUC] curve 0.78 vs. 0.81, $P = .048$) and French ACS patients (AUC 0.77 vs. 0.84; $P = .002$). The newly developed SEX-SHOCK score, now incorporating ST-segment elevation, creatinine, C-reactive protein, and left ventricular ejection fraction (LVEF), outperformed ORBI in both sexes (AUC females, 0.81; AUC males, 0.83; $P < .001$), also in internal and external validation in RICO (AUC

females, 0.82; AUC males, 0.88; $P < .001$) and SPUM-ACS (AUC females, 0.83, $P = .004$; AUC males, 0.83, $P = .001$) (*Figure 1*).

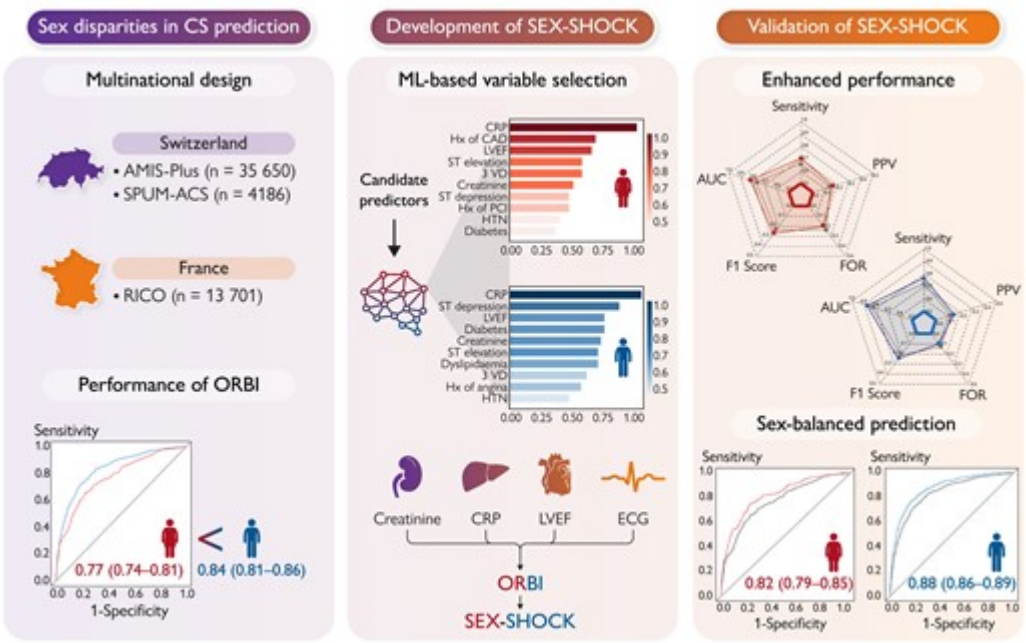

Figure 1

This multinational study evaluates the sex-specific performance of the ORBI risk score in predicting in-hospital cardiogenic shock (CS) complicating acute coronary syndromes (ACS), and provides a novel score (i.e. SEX-SHOCK), now accounting for sex-specific disease and management characteristics. By leveraging machine learning (ML) and regression-based approaches, novel candidate predictors of CS were identified (i.e. creatinine, C-reactive protein [CRP], left ventricular ejection fraction [LVEF], and ST-segment elevation) and SEX-SHOCK was developed, and internally and externally validated. The SEX-SHOCK score outperforms ORBI in both sexes, showing improved performance for the prediction of in-hospital CS in females and males alike; thus, SEX-SHOCK mitigates sex inequities in the acute management of patients with ACS. AUC, area under the receiver operating characteristic curve; CAD, coronary artery disease; ECG, electrocardiogram; FHx, family history; FOR, false omission rate; HTN, hypertension; MLP, multiple layer perceptron; PCI, percutaneous coronary intervention; PPV, positive predictive value; RF, random forest; VD, vessel disease1

Wang *et al.* conclude that the ORBI score shows modest sex-specific performance. The novel SEX-SHOCK score provides superior performance in females and males across the entire spectrum of ACS, thus providing a basis for future interventional trials and contemporary ACS management. The contribution is accompanied by an **Editorial** by Karl-Patrik Kresoja and Holger Thiele from the University of Leipzig, Germany, and Maria Rubini Giménez from the Centro Nacional de Investigaciones Cardiovasculares (CNIC) in Madrid, Spain.7 The authors highlight that as we strive to advance our tools and techniques, we must remain vigilant, always questioning whether the elegance of a model is matched by its utility. Just as the Emperor's subjects learned to see through the illusion, we too must ensure that our clinical decisions are guided by clear-sighted assessment, balancing the potential benefits of prediction against the practicalities of application. In the end, the true measure of a score's worth lies not in the complexity of its construction, but in its capacity to genuinely improve patient care.

Antiplatet drugs play a key role in the prevention and treatment of cardiovascular diseases.8–14 Glycoprotein VI (GPVI) is a platelet collagen/fibrin(ogen) receptor and an emerging pharmacological target for the treatment of thrombotic and thromboinflammatory diseases, notably ischaemic stroke. In a Fast Track Clinical Research article entitled **'The humanized platelet glycoprotein VI Fab inhibitor EMA601 protects from arterial thrombosis and ischaemic stroke in mice'**, Stefano Navarro from the Institute of Experimental Biomedicine I in Würzburg, Germany, and colleagues, developed a novel humanized anti-GPVI antibody Fab fragment (EMA601; K_D: 0.195 nM) that inhibits hGPVI function with very high potency *in vitro* and *in vivo*.15 Fab fragments of mouse anti-hGPVI IgG (Emf6.1Fab) were tested for functional GPVI inhibition in human platelets and in hGPVI-expressing (*hGP6tg/tg*) mouse platelets. The *in vivo* effect of Emf6.1Fab was assessed in a tail bleeding assay, an arterial thrombosis model, and the transient middle cerebral artery occlusion (tMCAO) model of ischaemic stroke. Using complementary-determining region grafting, a humanized version of Emf6.1Fab (EMA601) was generated.

Emf6.1Fab/EMA601 interaction with hGPVI was mapped in array format and kinetics, and quantified by biolayer interferometry. Emf6.1Fab (K_D: 0.427 nM) blocked GPVI function in human and *hGP6tg/tg* mouse platelets in multiple assays *in vitro* at concentrations ≥5 µg/mL. Emf6.1Fab (4 mg/kg)-treated *hGP6tg/tg* mice showed potent hGPVI inhibition *ex vivo* and were profoundly protected from arterial thrombosis as well as from cerebral infarct growth after tMCAO, whereas tail-bleeding times remained unaffected. Emf6.1Fab bound to a so far undescribed membrane-proximal epitope in GPVI. The humanized variant EMA601 displayed further increased affinity for hGPVI (K_D: 0.195 nM) and fully inhibited the receptor at 0.5 µg/mL, corresponding to a > 50-fold potency compared with ACT017, a GP inhibitor tested in early human trials.

Navarro *et al.* conclude that EMA601 is a conceptually novel and promising antiplatelet agent to efficiently prevent or treat arterial thrombosis and thromboinflammatory pathologies in humans at risk. The contribution is accompanied by an **Editorial** by James D. McFadyen, Xiaowei Wang, and Karlheinz Peter from the University of Melbourne in Australia.16 The authors note that for the highly encouraging findings from Navarro and colleagues, the ultimate challenge is now whether their high-affinity GPVI inhibition can be translated into clinical application. Indeed, whilst the safety profile of GPVI-targeting approaches in clinical trials is highly reassuring, given the demonstrated increased potency of EMA601, its safety profile will require meticulous clinical evaluation. This is particularly important in stroke where there is intense interest in adjunct antithrombotic strategies to augment the efficacy of pharmacological and interventional reperfusion strategies. However, for such an approach to be feasible, safety is paramount given the potentially significantly deleterious clinical consequences from even small intracranial haemorrhages. However, ultimately it must be acknowledged that the clinical efficacy of GPVI inhibition remains an unanswered question. Whilst ongoing trials with glencozimab in the treatment of stroke (GREEN study) and myocardial infarction (MI) (LIBERATE study) will provide further information, the

development of EMA601 as a novel, potentially more potent and mechanistically different GPVI inhibitor will be an important step either on the path to the holy grail, or the realization that mythical objects remain out of reach.

Somatic mutations in the *TET2* gene that lead to clonal haematopoiesis (CH) are associated with accelerated atherosclerosis development in mice and a higher risk of atherosclerotic disease and other cardiac diseases in humans.17 Mechanistically, these observations have been linked to exacerbated vascular inflammation. In a Fast Track Clinical Research article entitled **'Colchicine prevents accelerated atherosclerosis in TET2-mutant clonal haematopoiesis'**, María Zuriaga from the Centro Nacional de Investigaciones Cardiovasculares (CNIC) in Madrid, Spain, and colleagues aimed to evaluate whether colchicine, a widely available and inexpensive anti-inflammatory drug, prevents the accelerated atherosclerosis associated with TET2-mutant CH.18 In mice, *TET2*-mutant CH was modelled using bone marrow transplantations in atherosclerosis-prone *Ldlr*−/− mice. Haematopoietic chimeras carrying initially 10% *Tet2*−/− haematopoietic cells were fed a high-cholesterol diet and treated with colchicine or placebo. In humans, whole-exome sequencing data and clinical data from >37 000 participants in the Mass General Brigham Biobank and >437 000 participants in the UK Biobank were analysed to examine the potential modifying effect of colchicine prescription on the relationship between CH and MI. Colchicine prevented accelerated atherosclerosis development in the mouse model of *TET2*-mutant CH, in parallel with suppression of interleukin-1β overproduction in conditions of TET2 loss of function. In humans, patients who were prescribed colchicine had attenuated associations between *TET2* mutations and MI. This interaction was not observed for other mutated genes.

The authors conclude that these results highlight the potential value of colchicine to mitigate the higher cardiovascular risk of carriers of somatic *TET2* mutations in blood cells, setting the basis for the development

of clinical trials that evaluate the efficacy of precision medicine approaches tailored to the effects of specific mutations linked to CH.

Risk stratification of sudden cardiac death after MI and prevention by defibrillator rely on LVEF. In a Clinical Research article entitled **'Sudden cardiac death after myocardial infarction: individual participant data from pooled cohorts'**, Niels Peek from the University of Manchester in the UK, and colleagues point out that improved risk stratification across the whole LVEF range is required for decision-making on defibrillator implantation.19 The analysis pooled 20 datasets with >140 000 post-MI patients containing information on demographics, medical history, clinical characteristics, biomarkers, electrocardiography, echocardiography, and cardiac magnetic resonance imaging. Separate analyses were performed in patients (i) carrying an implantable cardioverter-defibrillator (ICD) for primary prevention with LVEF ≤35% (ICD patients), (ii) without ICD with LVEF ≤35% (non-ICD patients ≤35%), and (iii) without ICD with LVEF >35% (non-ICD patients >35%). Primary outcome was sudden cardiac death or, in defibrillator carriers, appropriate defibrillator therapy. Using a competing risk framework and systematic internal–external cross-validation, a model using LVEF only, a multivariable flexible parametric survival model, and a multivariable random forest survival model were developed and externally validated. Predictive performance was assessed by random effect meta-analysis. There were 1326 primary outcomes in ICD patients, 1193 in non-ICD patients ≤35%, and 1567 in non-ICD patients >35% during a mean follow-up of 30, 46, and 57 months, respectively. In these three subgroups, LVEF poorly predicted sudden cardiac death (*c*-statistics between 0.50 and 0.56). Considering additional parameters did not improve calibration and discrimination, and model generalizability was poor.

The authors conclude that more accurate risk stratification for sudden cardiac death and identification of low-risk individuals with severely reduced LVEF or of high-risk individuals with preserved LVEF is not currently feasible, neither using LVEF nor using other predictors. This manuscript is accompanied by an **Editorial** by Ezimamaka Ajufo and Usha Tedrow from

the Harvard Medical School in Boston, MA, USA.20 The authors conclude by congratulating the authors on using the present work as a starting point to further explore novel patient selection strategies in the prospective, Prevention of Sudden Cardiac Death after Myocardial Infarction by Defibrillator Implantation (PROFID EHRA) trial (NCT 05665608), which will assess the incremental value of primary prevention ICD therapy in contemporary patients on optimal medical therapy post-MI.

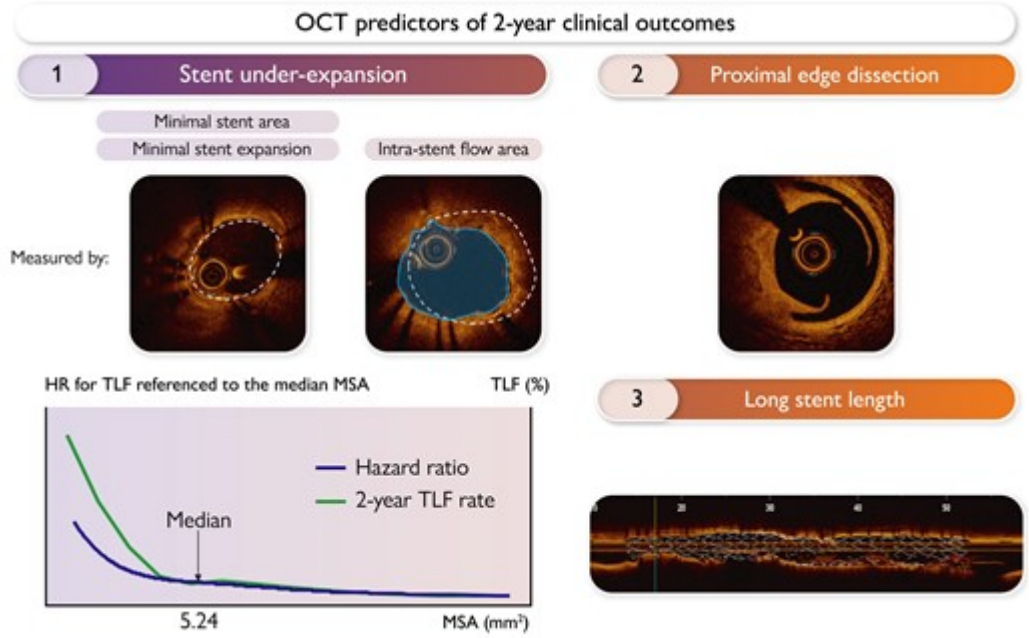

Figure 2

The independent optical coherence tomography predictors of clinical outcomes in 2128 patients with a single treated lesion in the ILUMIEN IV trial are shown here. Minimal stent area is defined as the smallest stent area within the contiguous stent segment. Minimal stent expansion is defined as the minimal stent area divided by the average of proximal and distal reference lumen areas × 100. Intra-stent flow (lumen) area is defined as stent area minus intra-stent plaque protrusion or thrombus area. HR, hazard ratio; ID-TLR, ischaemia-driven target lesion revascularization; MSA, minimal stent area; MSE, minimal stent expansion; OCT, optical coherence tomography; TLF, target lesion failure; TV-MI, target-vessel myocardial infarction21

Observational registries have suggested that optical coherence tomography (OCT) imaging-derived parameters may predict adverse events after drug-eluting stent (DES) implantation. In another Clinical Research article entitled **'Optical coherence tomography predictors of clinical outcomes after stent implantation: the ILUMIEN IV trial'**, Ulf Landmesser from the Charité–Universitätsmedizin Berlin in Germany, and colleagues sought to determine the OCT predictors of clinical outcomes in this post-hoc analysis of the large-scale ILUMIEN IV trial.21 ILUMIEN IV was a prospective, single-blind trial of 2487 patients with diabetes or high-risk lesions randomized to OCT-guided vs. angiography-guided DES implantation. All patients underwent final OCT imaging (blinded in the angiography-guided arm). From >20 candidates, the independent OCT predictors of 2-year target lesion failure (TLF; the primary endpoint), cardiac death or target-vessel MI (TV-MI), ischaemia-driven target lesion revascularization (ID-TLR), and stent thrombosis were analysed by multivariable Cox proportional hazard regression in single treated lesions. A total of 2128 patients had a single treated lesion with core laboratory-analysed final OCT. The 2-year Kaplan–Meier rates of TLF, cardiac death or TV-MI, ID-TLR, and stent thrombosis were 6.3, 3.3, 4.3, and 0.9%, respectively. The independent predictors of 2-year TLF were a smaller minimal stent area (per 1 mm2 increase: hazard ratio 0.76, $P < .0001$) and proximal edge dissection (hazard ratio 1.77, $P = .004$). The independent predictors of cardiac death or TV-MI were smaller minimal stent area and longer stent length. The independent predictors of ID-TLR were smaller intra-stent flow area and proximal edge dissection; and of stent thrombosis was smaller minimal stent expansion (*Figure 2*).

The authors conclude that in the ILUMIEN IV trial, the most important OCT-derived post-DES predictors of both safety and effectiveness outcomes are parameters related to stent area, expansion, proximal edge dissection, and stent length. The contribution is accompanied by an **Editorial** by Enrico Romagnoli, Mattia Lunardi, and Francesco Burzotta from the Fondazione Policlinico Universitario A. Gemelli IRCCS in Rome, Italy.22 The authors

note that although we are still awaiting definitive proof of the net clinical benefit of intravascular imaging in percutaneous coronary intervention (PCI) existing data confirm the overall intraprocedural positive impact of OCT guidance. Thus, in the meantime, the optimization of some specific post-stenting OCT parameters might be incorporated into daily PCI practice. Despite use of a rigorous methodology, uncertainty remains about which combination of parameters provides the most valuable information and best correlates with clinical outcome.

Proteomics is playing a growing role in risk prediction,23,24 but only few population-based cohort studies, including both men and women, have explored circulating proteins associated with incident MI. In a further Clinical Research article entitled **'Plasma proteome and incident myocardial infarction: sex-specific differences'**, Olga Titova from the Uppsala University in Sweden, and colleagues investigated the relationships between circulating cardiometabolic-related proteins and MI risk using cohort-based and Mendelian randomization (MR) analyses, and explored potential sex-specific differences.25 The discovery cohort included >11 500 Swedish adults. Data on 259 proteins assessed with Olink proximity extension assays, biochemical, and questionnaire-based information were used. Participants were followed-up for incident MI and death over 8 years through linkage to Swedish registers. Replication analyses were conducted on the UK Biobank sample. In MR analyses, index *cis*-genetic variants strongly related to the proteins were used as instrumental variables. Genetic association summary statistic data for MI were obtained from the CARDIoGRAMplusC4D consortium and FinnGen. Forty-five proteins were associated with incident MI in discovery and replication samples following adjustment for potential confounders and multiple testing. In the secondary analysis, 13 of the protein associations were sex specific, with most associations identified among women. In MR analysis, genetically predicted higher levels of renin, follistatin, and retinoic acid receptor responder protein 2 were linked to an increased risk of MI. Tissue factor pathway

inhibitor, tumour necrosis factor receptors 1 and 2, and placenta growth factor had an inverse association with MI.

The authors conclude that this study both identifies new associations and confirms previously established associations between circulating proteins and incident MI and, for the first time, suggests sex-specific patterns in multiple protein–MI associations. The manuscript is accompanied by an **Editorial** by Anna Barton from the University of Edinburgh, UK, Emily Lau from the Massachusetts General Hospital in Boston, MA, USA, and Martha Gulati from the Cedars-Sinai Medical Center in Los Angeles, CA, USA.26 The authors highlight that Titova and colleagues present a well-conducted analysis examining the association of proteins with future MI and have demonstrated notable sex differences in the association between proteins and future MI, with potential causality suggested for many of these identified proteins. Despite limitations related to external validity, these findings are an important addition to the currently limited body of evidence examining mechanisms of sex-based differences in cardiovascular disease (CVD). The proteins identified in this analysis shed light on the biological pathways that drive MI development in males and females and may serve as potential targets for both preventive and therapeutic intervention. The authors hope that continued efforts to leverage molecular profiling to rigorously elucidate mechanisms driving CVD in females and further inclusion of females in clinical trials will allow us to forget Yentl syndrome in the near future.

8. Enrollment of Females in Randomized Trials for Glucagon-Like Peptide 1 Receptor Agonists: A Systematic Review

Introduction

Cardiovascular disease (CVD) remains the leading cause of death among females.**1-7** Despite significant improvements in available therapeutics for CVD, cardiovascular (CV) mortality in females has been increasing over the

last decade.**1** Females with CVD have been historically underrecognized and underrepresented in heart failure (HF), coronary artery disease, and acute coronary syndrome randomized controlled trials (RCTs).**8** Furthermore, over the past 2 decades, females have remained inadequately represented in renal and cardiometabolic trials.**2**,**4**,**9-11** This problem has persisted despite recommendations by the regulatory and funding institutions to promote diversity and equity in RCTs.**10**,**12-15** These points are crucial because the treatment effects established in most RCTs where majority of participants were men do not mirror the diverse treatment responses seen when we account for the wide-ranging demographic groups in CV trials.**12** The movement for inclusion of females in research started in 1985 when the Assistant Secretary of Health, Edward N. Brandt Jr, appointed a Task Force to identify health issues especially in conducting research and evaluation.**16** This led the National Institutes of Health advisory committee to recommend the inclusion of females in research in 1993.**17**

In recent years, there has been a paradigm shift in the management of diabetes mellitus (DM) with the introduction of glucagon-like peptide 1 receptor agonists (GLP-1RAs).**18** These antihyperglycemic agents have been proven to be effective in weight reduction among patients with obesity, and additionally have been demonstrated to reduce CV events among obese patients with DM, and in patients with chronic kidney disease (CKD), and HF.**6**,**18**

Population trends show that the prevalence of obesity and severe obesity is increasing in females.**19** Furthermore, while the age-adjusted prevalence between males and females is similar, the prevalence of obesity in females is higher than in males among those >60 years of age.**19** Moreover, the prevalence of severe obesity (Body mass index >40 kg/m2) is higher in females versus males (12% vs 7%), with the highest prevalence of severe obesity found in Black females (19%).**19**

While the proportion of females enrolled in GLP-1RA landmark CV trials is already established,**7** the trend of female enrollment in GLP-1RA RCTs from

approval until present is still unknown. Hence to address this knowledge gap, we performed a trend analysis of the prevalence of females in GLP-1RA RCTs from 2008 to 2023. Furthermore, we also determine the representation of females relative to their disease burden.

Methodology

The data that support the findings of this study are available from the corresponding author upon reasonable request. Approval from the Institutional Review Board was not required for this study as publicly available data were utilized. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO),**20** with the identification number **CRD42024542778**.

Data sources and searches

The literature search was performed using PubMed/MEDLINE, Ovid/Embase, Google Scholar, and clinicaltrials.gov from database inception until April 2024. Search terms included “glucagon-like peptide-1 receptor agonists,” “GLP-1 agonist," “GLP-1RA,” “semaglutide,” “dulaglutide,” “albiglutide,” “exenatide,” “liraglutide,” “lixisenatide,” “efpeglenatide,” “placebo,” “cardiovascular disease,” “cardiovascular risk factors,” “randomization,” “clinical trials,” “intervention studies,” and synonyms. Citations of selected articles and any relevant studies that evaluated GLP-1RA and CV outcomes were reviewed. After removing duplicates, records were reviewed at the title and abstract level, followed by the screening of full text based on our study criteria. If a trial did not reach the analysis phase, it was excluded from our study. Data for each randomized trial were abstracted for each study and subsequently grouped by year of publication.

Study selection

The prespecified inclusion criteria were as follows: 1) cardiometabolic RCTs on GLP-1RA; 2) sample size of at least 100 participants and follow-up duration of at least 12 weeks; and 3) English language. As with the previous

published pooled studies,**21**,**22** we selected large RCTs with follow-up periods of 12 weeks. The treatment was either monotherapy of GLP-1RA or added GLP-1RA to nonrandomized background hypoglycemia treatments. The comparator could be a placebo or any antidiabetic medications. We excluded RCTs performed among patients younger than 18 years, and those reporting secondary, interim, or post hoc analyses. We also excluded open-label extension trials and those RCTs wherein GLP-1RA are mixed with insulin or other antidiabetic agents as 1 drug preparation. Lastly, our study focused mainly on pure GLP-1RAs; hence, we did not include tirzepatide and other dual agents (**Supplemental Figure 1**).

Data extraction

Key participant and intervention characteristics and reported data on efficacy outcomes were extracted independently by 2 investigators (M.C.Y. and J.M.) using standard data extraction templates. Any disagreements were resolved by discussion or, if required, by a third author (F.B.R.). Data on the following variables were extracted: first author's name, year of publication, journal, study phase, interventional and control treatments, randomization method, analysis tool, number of randomized patients, and demographic and clinical data including proportion reporting results based on sex and age, and inclusion and exclusion criteria that would limit the recruitment of women. We also categorized RCTs according to therapy, setting, target population or indication, and location. In case of uncertainties regarding the study data, we contacted the authors of the specific study for additional information. Quality assessment was performed independently by 2 review authors using the Revised Cochrane risk-of-bias tool for randomized trials.

Outcome measures

The primary endpoint of this systematic review was the prevalence of females in GLP-1RA RCTs across time and mean age of participants. Subgroup analyses was done to identify differences in prevalence of females

in type of GLP-1RA received, diabetes status, indication of therapy, and concurrent comorbidities. Secondary endpoints include representation of females in GLP-1RA RCTs relative to their disease burden expressed as participation to prevalence ratio (PPR).

Statistical analysis

Descriptive statistics for categorical variables were expressed as aggregated counts or percentages; and continuous variables were expressed using mean ± SD or median (IQR). Categorical variables were compared using Pearson chi-square, Fisher's exact, and Kruskal-Wallis tests. Continuous variables (age, duration of treatment, and follow-up) were compared over time (year of publication) using Cuzick's nonparametric trend test, correcting for the total population per study. Since it was not possible to compute for the I2, we determined the degree of heterogeneity based on the CIs.

The proportion of females among the total participants was extracted per study. This was compared over time (year) of publication and over mean age of participants, using Cuzick's nonparametric trend test, correcting for the total population per study. This proportion was also compared between specific types of GLP-1RA received, diabetes status, indication of therapy, concurrent comorbidity using Wilcoxon rank sum, and Kruskal-Wallis tests. Finally, correlation between the continuous variables age, treatment duration, and follow-up duration (in weeks) and the proportion of females in clinical trials was determined using Spearman rank correlation test.

In order to compare participation of females in clinical trials to the actual numbers of females affected by disease, the metric PPR was used, which is computed by dividing the proportion of females among participants in the clinical trials included in this study, to the latest available epidemiologic population-based data on the sex-specific prevalence for these diseases among females. A PPR of <0.8 indicates underrepresentation; approximately equal to 1.0 indicates adequate representation, and >1.2 indicates overrepresentation. Two-sided hypotheses testing was performed with level

of significance set at $\alpha<0.05$. Statistical analyses were performed using STATA MP, version 14.0 and Microsoft Excel.

Results

General characteristics

After screening 4,178 studies for eligibility and removal of duplicates, 98 RCTs with 186, 396 participants were included in our analysis. Significant heterogeneity was found among included studies. The descriptive statistics for these RCTs are found in **Table 1**. Overall, 73,897 (39.6%) females were included. For each RCT, the median number of participants is 520 (IQR: 295-1,202). Fifteen (15.3%) RCTs with 32,006 (17.17%) participants were done on semaglutide. Eighteen (18.37%) RCTs with 20,150 (10.81%) participants were done on exenatide. Eleven (11.22%) RCTs with 14,599 (7.83%) participants were on albiglutide. Thirty-three (33.67%) RCTs with 71,985 (38.62%) participants received liraglutide. Twelve (12.24%) RCTs with 28,763 (15.43%) participants received dulaglutide. Seven (7.14%) RCTs with 14,411 (7.73%) participants received lixisenatide. Lastly, 2 (2.04%) RCTs with 4,482 (2.40%) participants received efpeglenatide.

Profile of participants by age and comorbidity

The mean age of the participants was 61.2 ± 5.3 years old, with a note of increasing trend over time (np-trend z = 2.35, P = 0.019), see **Figure 1**. Majority, or 82 (84.69%) of RCTs with 160, 742 (86.23%) participants were done among patients with DM, while 15 (15.30%) RCTs with 25,654 (13.76%) participants were done among those without. Patients with DM were significantly older (age 61.9 ± 0.01 years) compared to those without (age 57.1 ± 0.04 years), z = 3.622, $P < 0.01$.

Important comorbidities include obesity (13 [13%] RCTs with 25,611 [14%] participants), coronary heart disease (CHD) (7 [7%] RCTs with 32,423 [17%] participants), HF (3 [3%] RCTs with 1,605 [1%] participants), and CKD

(3 [3%] RCTs with 1,578 [1%] participants). The mean age significantly differs between these comorbidity groups (Pearson chi-square = 29.32, $P < 0.01$); patients who are obese are the youngest (56.8 ± 0.05) followed by those without comorbidities (61.39 ± 0.01); those with CHD (63.26 ± 0.02), and CKD (63.87 ± 0.01) have comparable ages, and patients with HF are the oldest (65.53 ± 0.06).

Cardiometabolic disease reduction is now the prevailing indication for GLP-1 receptor antagonist trials, with 114,489 (61%) participants in 21 (21.4%) RCTs, followed by DM with 45,511 (24%) participants in 62 (63%) of RCTs, and weight loss, with 26,396 (14%) participants in 15 (15.30%) RCTs. Treatment duration in weeks (Pearson chi-square = 20.5, $P = 0.15$, np-trend by year $z = 1.29$, $P = 0.196$) and follow-up duration in weeks (Pearson chi-square = 16.9, $P = 0.32$, np-trend by year $z = 1.91$, $P = 0.056$) were comparable across studies and over time.

Trends in trials reporting outcomes based on sex

In our study, only 2 RCTs reported sex-specific outcomes (2%). Both these studies were studies in females without diabetes. The study of Elkind-Hirsch et al (2021)**23** used exenatide among females with polycystic ovary syndrome, while Rodgers et al (2021)**24** used exenatide among overweight and obese females for weight loss. The other studies did not report sex-specific outcomes.

Prevalence of female participants

The 98 RCTs were able to enroll 73,897 females, comprising 39.7% of the total study population. The proportion of females in RCTs, stratified by subgroup, is described in detail in **Table 2**. The representation of females did not significantly differ across different GLP-1RA RCTs (Pearson chi-square = 2.31, $P = 0.89$). Studies done on patients without DM had a higher proportion of females in their total study population (42%) compared to those studies done among patients with DM (39%) ($z = 4.53$, $P < 0.01$) (**Figure 2**). The representation of females is also different across the major

comorbidities, apart from DM, that was described. Studies done on patients with CHD have a lower proportion of females (35%) compared to those done for obesity (42%), HF (42%) and those with no comorbidity (40%). The limited studies that were included concerning CKD had good representation of females (46%) compared to the rest mentioned (Pearson chi-square = 29.32, $P < 0.01$) (**Figure 3**).

Table 2Subgroup Analyses of Proportion of Females in RCTs	**N**	**Females**	**F/N ratio**	***P* Value**
Therapy				
Semaglutide	32,006	11,240	0.35	0.89
Exenatide	20,150	8,127	0.40	
Albiglutide	14,599	5,155	0.35	
Liraglutide	71,985	29,448	0.41	
Dulaglutide	28,763	13,494	0.47	
Lixisenatide	14,411	4,902	0.34	
Efpeglenatide	4,482	1,531	0.34	
By DM				
Non-DM	25,654	10,882	0.42	<0.01
DM	160,742	63,015	0.39	
By indication				
Obesity	26,396	11,180	0.42	<0.01
Diabetes	45,511	20,333	0.45	
Cardiovascular-metabolic	114,489	42,384	0.37	
By comorbidity				
None	115,413	46,638	0.40	<0.01
Obesity	25,611	10,861	0.42	
Coronary heart disease	32,423	11,431	0.35	
Heart failure	1,605	675	0.42	
Others	9,766	3,559	0.36	
CKD	1,578	733	0.46	

CKD = chronic kidney disease; RCT = randomized controlled trials; other abbreviations as in **Table 1**.

Temporal trends in female participants

Over time, there is a significant decline observed in the proportion of females enrolled in RCTs compared to men (np-trend $z = -2.29$, $P = 0.022$) (**Table 1**, **Figure 4**). This could be explained by the observation that more cardiometabolic studies have been done in the last 5 years that have less proportion of females (35%) compared to studies done for obesity (42%) or diabetes treatment (45%) (Pearson chi-square = 25.95, $P < 0.01$) (**Table 2**). This is also consistent with the lower proportion of females in studies concerning CHD, as described earlier. We also found out that studies done on older participants tend to have a lower proportion of females (np-trend $z = -2.76$, $P < 0.001$) (**Figure 5**).

Representation of females in trials compared with their disease burden

Globally, females were underrepresented compared with their share of the disease population in trials of CHD (PPR, 0.72). There was fair representation of females with their share of the disease population both in the United States and globally for DM (U.S. PPR, 0.89; global PPR, 0.81), HF (U.S. PPR, 0.94; global PPR, 0.83), CHD (U.S. PPR 0.82), and obesity (U.S. PPR 1.0). However, for trials on obesity, females were overrepresented compared with their proportion in disease population globally (PPR, 2.27) (**Figure 6**, **Central Illustration**).

Discussion

In this trend analysis of enrollment of females in RCTs for GLP-1RA, we established that: 1) females comprised 40% of the total RCT participants; 2) the proportion of female participants has been declining over time; 3) very few RCTs have sex-specific outcomes; 4) there was a lower proportion of

females for trials on CHD, HF, and obesity; and lastly, 5) globally, females were underrepresented compared with their share of the disease population in trials of CHD.

There are established reasons that impede the involvement of females in RCTs, one of which is the trial inclusion and exclusion criteria. These screening processes that lead to a disproportionate exclusion of females are commonly influenced by the sex differences in biology and disease manifestation.**25**,**26** Consequently, the criteria for inclusion in these trials may inadvertently exclude females, leading to their underrepresentation. For example, criteria that exclude the elderly may indirectly result in the exclusion of women, as increasing age at trial enrollment was found to correlate with higher enrollment of females.**27-29** This may further widen the sex gap in mortality outcomes, as the prevalence of obesity is higher in women older than 60 years old.**19** These highlight the importance of considering sex-specific factors in trial design and recruitment strategies to ensure equitable representation and accurate assessment of treatment efficacy across populations. Trials may be designed to accommodate more flexible visit schedules, offset hidden costs of participation such as transportation and care-giver arrangements, and incorporate the perspective of women participants in the conduct of the study.**30** Contrary to this hypothesis, Scott et al (2018)**10** established that only a small number of female RCT participants are being eliminated during the screening process, demonstrating that factors occurring prior to screening including historical bias, safety concerns, hormone variability, socioeconomic factors, and recruitment strategies may play a more vital role in the underrepresentation of females in RCTs. While current understanding acknowledges the importance of adequate inclusion of females in clinical trials, traditionally, medical research has had particularly noticeable biases in diseases that are prevalent in both sexes and has focused more on men due to the misconception that their physiology is representative of the general population.**31** Concerns about potential risks to women of childbearing age, particularly during pregnancy, have led to policies categorizing pregnant

women as part of the vulnerable population, driving researchers to exclude them from trials to avoid potential complications.**17**,**32**,**33** The Thalidomide Tragedy serves as an example of the devastating consequences of utilization of novel drugs during pregnancy.**34**,**35** Incidents like this have raised the challenge of balancing the potential benefits to the mother against the risks to the fetus, or vice versa, resulting in an overly cautious approach wherein researchers prefer to avoid ethical debates and adverse publicity. In relation to this, the menstrual cycle and hormonal fluctuations in females have been known to introduce variability in study outcomes. Various studies especially after the menstrual changes observed during COVID-19 vaccination clinical trials are pushing for adding menstrual cycle status as the fifth vital sign and encouraging its inclusion in the standard methods of performing clinical trials.**36** Another example is the standard approach in conducting studies on vascular function which typically involves regulating the menstrual cycle phase of participants; specifically, testing females during the early follicular phase.**37** These demonstrate that females may be more confounding and more expensive test subjects, leading some researchers to avoid including females in trials to simplify data analysis.

Females may also face barriers to participation in clinical trials due to socioeconomic factors such as lack of access to transportation or childcare, caregiving responsibilities, and employment constraints.**38** Traditional recruitment strategies may not effectively reach females, particularly those from underrepresented communities. Cultural and language barriers, as well as mistrust of the medical system, can further hinder recruitment efforts. Women were found to be less willing to participate in CV trials than men, partly due to perceived greater risk of harm in participating.**39**,**40** Increasing the number of women enrolled in clinical trials requires identifying potential barriers to female trial participation.**41** In addition, the number of female trial investigators/authors plays an important role in recruiting more women to enroll in trials, as studies have shown a direct correlation between the two.**30**,**42**,**43** An ongoing study, the WIN-Her Initiative (Women Opt-In for

Heart Research), is currently exploring women's attitudes toward participation in clinical trials and has identified several potential barriers, such as minimal understanding of trial logistics, misperceptions of trial participation risks and benefits, and limited trial information offered by clinicians.**27**,**41**

Another related concept being explored is the societal and cultural misogyny that perpetuates the perception of females as "difficult," where their primary role and responsibility in life is to preserve fertility and esthetic standards.**44** The androcentric bias of medical knowledge and practice may manifest in health care providers attributing females' symptoms to psychological factors or dismissing their concerns, leading to disparities in diagnosis, treatment, and outcomes.**45**

The Food and Drug Administration (FDA) has made continuous concerted efforts to enhance the inclusion of females in clinical trials to ensure that medical products are safe and effective for all populations. The agency has issued guidance and protocols that emphasize the importance of including females in clinical trials across all phases of drug development.**17** These documents provide recommendations for sponsors on how to design and conduct studies that adequately represent both genders. The FDA has also implemented requirements that mandate the inclusion of females in clinical trials unless there are scientifically justifiable reasons for their exclusion, ensuring that sex representation is considered during the drug development process.**46** To further reinforce these efforts, the FDA conducts campaigns and programs that aim to raise awareness among researchers, sponsors, and Institutional Review Boards about the importance of including females in clinical trials by providing resources and training on sex-specific considerations in clinical research.**47** Additionally, the FDA has also implemented a system to monitor and address disparities in representation, which involves analyzing clinical trial data and requiring sponsors to report demographic information, including sex, in their submissions.**48**,**49** Lastly, the FDA works with patient advocacy groups, professional organizations, and academic institutions to promote the inclusion of females in clinical

trials.**47** These partnerships help facilitate discussions, share best practices, and address barriers to participation.

The underrepresentation of females in clinical research has profound implications for the advancement of medical knowledge and the development of sex-specific health care interventions. Accordingly, females' unique health issues, biological differences, and responses to treatments may not be fully understood or adequately addressed. One significant consequence of this disparity is the lack of generalizability of research findings to females.**47**,**50** This contributes to gaps in understanding sex-specific health issues and disparities in health care outcomes.

Overall, the underrepresentation of females in clinical trials represents a significant barrier to achieving gender equity in health care.**15** Addressing this issue requires concerted efforts to increase the inclusion of females in research studies, prioritize sex-specific health research, and ensure that research findings are applicable and beneficial to women's health. Novel strategies to recruit and enroll women in CV trials must be developed and implemented. By closing the gender gap in clinical research, health care outcomes for women and health equity for all can be improved.

Moving forward, efforts to address the underrepresentation of females in clinical research should focus on promoting equity, inclusivity, and diversity in health care research. This includes advocating for the inclusion of females from diverse backgrounds, including racial and ethnic minorities, LGBTQ + individuals, and individuals with disabilities. By ensuring that research studies reflect the equity and diversity of the population, studies can generate findings that are more applicable, accessible, and beneficial to all individuals. Lastly, while we established decreasing trend in enrollment among females in GLP-1RA trials, current real-world data have shown more pronounced use of GLP-1RA among females than males.**51-53**

Strengths and limitations

To our knowledge, this is the first systematic review to comprehensively report on the trends of enrollment of females in GLP-RA RCTs. Our study has several major limitations. This is a study-level systematic review, and we could not access individual patient data. Moreover, because only 2 RCTs reported sex-specific outcomes, it was not ideal to perform a subgroup analysis. Furthermore, because majority of trials from 2007 to 2024 did not report disaggregated data on race/ethnicity, we failed to obtain a significant number of trials that we can meaningfully analyze. For this reason, we did not examine the enrollment trends of participants from ethnic and racial minority groups.

Conclusions

In this trend analysis, we explored the representation of females in GLP-1RA RCTs. Females comprised less than half of the total population. The proportion of female participants has also been declining over time. Furthermore, there was a lower proportion of females for trials on CHD, HF, and obesity. Lastly, females were underrepresented in RCTs compared with their relative disease burden in the population.

9. Pregnancy-Related Mortality Due to Cardiovascular Conditions: Maternal Mortality Review Committees in 32 U.S. States, 2017 to 2019

Introduction

The pregnancy-related mortality ratio in the United States has not improved over the last 20 years.**1** Considerable racial-ethnic disparities in pregnancy-related mortality persist, with pregnancy-related mortality ratios among non-Hispanic Native Hawaiian or other Pacific Islander persons 4 times higher, non-Hispanic Black persons 3 times higher, and non-Hispanic American Indian or Alaska Native persons 2 times higher than among non-Hispanic White persons.**1**

Maternal Mortality Review Committees (MMRCs) provide a deep understanding of pregnancy-related mortality through detailed case reviews by a multidisciplinary group of clinical and nonclinical individuals.**2** A recent report from MMRCs in 36 states identified differences in the leading underlying cause of pregnancy-related death by race-ethnicity.**3** Overall, cardiac and coronary conditions (excluding cardiomyopathy [CM]) and CM were the second most frequent underlying cause of pregnancy-related deaths (20.6%) and among non-Hispanic Black persons, they were the most frequent underlying causes, accounting for 30% of pregnancy-related deaths.**3** A prior analysis of cardiovascular deaths from a state-based MMRC found that the majority of deaths were due to acquired heart disease, with CM the most common etiology.**4**

The purpose of this analysis is to provide demographic and clinical information on specific cardiovascular causes of pregnancy-related deaths, to identify factors contributing to these deaths, and share example recommendations made by MMRCs to reduce preventable cardiovascular deaths among the most frequently identified contributors.

Methods

Study design and population

Using Maternal Mortality Review Information Application (MMRIA) data shared with the Centers for Disease Control and Prevention (CDC) by MMRCs, we analyzed data from the 32 states contributing data with pregnancy-related deaths with an MMRC-determined cause of CM and other cardiovascular conditions (OCVs) occurring among residents from 2017 to 2019 (**Supplemental Appendix**). In some states, only partial years of data were shared. We refer to the combination of CM and OCV as cardiovascular conditions (CV). This study did not involve human subjects as defined in 45 CFR 46.102(e) and therefore was not reviewed by an Institutional Review Board.

Variables

Race and ethnicity were derived from the birth or fetal death record. If missing on the birth or fetal death record or if a linked birth or fetal death record was not available, race and ethnicity were derived from the death record and classified as Hispanic, non-Hispanic American Indian or Alaska Native, non-Hispanic Asian, non-Hispanic Black, non-Hispanic Native Hawaiian or other Pacific Islander, non-Hispanic White, or non-Hispanic another/multiple races using previously described methods.**3** Age at death was based on the death record and categorized as ages 15 to 19 years, 20 to 24 years, 25 to 29 years, 30 to 34 years, 35 to 39 years, 40 to 44 years, and 45 years and older.

Methods for determining timing of death in relation to pregnancy have been described previously.**3** Briefly, timing of death was assigned by using the number of days between the date of death and the end of pregnancy, as documented by the MMRC abstractor, or as calculated by using the number of days between the date of death on the death record and the date of birth or fetal death on the linked birth or fetal death record by CDC.**3** If the specific number of days was missing, deaths that the MMRC abstractor classified as pregnant at the time of death, or with the standard pregnancy checkbox on the death certificate marked as pregnant at the time of death, were classified as during pregnancy.**3**

MMRCs determine a pregnancy-associated death (death during pregnancy or within 1 year of the end of pregnancy) to be pregnancy related if the death was from a pregnancy complication, a chain of events initiated by pregnancy, or the aggravation of an unrelated condition by the physiologic effects of pregnancy. The underlying cause of death is defined as the disease or injury which initiated the chain of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury. The MMRC-determined underlying cause of death 1) is coded using a standardized list of 20 major categories and 69 subcategories**3**,**5** and 2) may vary from official underlying cause of death documented on the death record due to the multidisciplinary review and additional information available to the MMRC.

CM includes deaths attributed to postpartum/peripartum CM, hypertrophic CM, and other CM/not otherwise specified (NOS). OCV includes deaths attributed to coronary artery disease/myocardial infarction/atherosclerotic cardiovascular disease, pulmonary hypertension, acquired and congenital valvular heart disease, vascular aneurysm/dissection, hypertensive cardiovascular disease, Marfan syndrome, conduction defects/arrhythmias, vascular malformations outside the head and coronary arteries, and cardiovascular/NOS (such as congestive heart failure, cardiomegaly, cardiac hypertrophy, cardiac fibrosis, and nonacute myocarditis). In a previous publication,**3** these deaths were titled "cardiac and coronary conditions." Hypertensive disorders of pregnancy (including gestational hypertension, preeclampsia, and superimposed preeclampsia) are disorders unique to pregnancy and are categorized separately. Cerebrovascular accidents are also categorized separately by MMRCs, and neither are included in this analysis.

MMRCs also make determinations for circumstances surrounding each death, including whether obesity, substance use disorder, and mental health conditions other than substance use disorder were a circumstance of the death. In May 2020, an additional field was added to the MMRIA Committee Decisions Form to document the MMRC determination of whether discrimination was a circumstance of the death.**5** Analysis of the discrimination circumstance was restricted to deaths reviewed by MMRCs after May 29, 2020. These circumstances are defined as whether obesity/substance use disorder/mental health condition/discrimination contributed to the death, and not just whether the circumstance was present.

A death is considered preventable if the MMRC determines there was at least some chance of the death being averted by one or more reasonable changes to patient, family, provider, facility, systems factors, and/or community.**3** If a death is determined to be preventable, the MMRCs describe, using free text, contributing factors, and recommendations among pregnancy-related deaths. For each contributing factor described, MMRCs

select a contributing factor class from a standardized list of 27 specific contributing factor classes. Each preventable pregnancy-related death can have multiple contributing factors and classes. MMRCs also make recommendations for preventing future pregnancy-related deaths for each contributing factor they identify.

For this report, we reviewed all MMRC recommendations among the 5 most common contributing factor classes. We selected example MMRC recommendations to represent each of the 5 most frequent contributing factor classes. MMRC recommendations included in this report may have been edited slightly for clarity.

Statistical analysis

Descriptive statistics were calculated as counts and percentages. Missing values are reported but not included in calculations of distributions. All analyses were performed using SAS, version 9.4 (SAS Institute Inc).

Results

Overall, there were 210 pregnancy-related deaths, which occurred in 2017 to 2019 among residents of the 32 states, with an MMRC-determined underlying cause of death attributed to CVs. This includes 84 (40.0%) pregnancy-related deaths with a CM as the underlying cause of death and 126 (60.0%) pregnancy-related deaths with an OCV as the underlying cause of death.

Demographic characteristics of the CV, CM, and OCV deaths are shown in **Table 1**. More than half of CM deaths (51.2%) were among non-Hispanic Black persons. Non-Hispanic Black and White persons each represented about 40% of OCV deaths. Among CV deaths overall, two-thirds (66%) occurred among people under the age of 35 years and 60% were among people with a high school education or less. Only 58% of the pregnancy-related CV deaths had an autopsy performed (**Table 1**).

Table 1Characteristics of Pregnancy-Related Total Cardiovascular Conditions, Cardiomyopathy, and Other Cardiovascular Conditions Deathsa	**Total Cardiovascular Conditions (N = 210)**	**Cardiomyopathy (n = 84)**	**Other Cardiovascular Conditions (n = 126)**
Race and ethnicity			
Hispanic	20 (9.8)	5 (6.1)	15 (12.2)
Non-Hispanic AI/AN	1 (0.5)	0 (0.0)	1 (0.8)
Non-Hispanic Asian	9 (4.4)	2 (2.4)	7 (5.7)
Non-Hispanic Black	90 (43.9)	42 (51.2)	48 (39.0)
Non-Hispanic NHOPI	0 (0.0)	0 (0.0)	0 (0.0)
Non-Hispanic White	82 (40.0)	33 (40.2)	49 (39.8)
Non-Hispanic all other/multiple races	3 (1.5)	0 (0.0)	3 (2.4)
Missing	5	2	3
Age (y)			
15-19	8 (3.8)	3 (3.6)	5 (4.0)
20-24	25 (12.0)	11 (13.1)	14 (11.2)
25-29	43 (20.6)	21 (25.0)	22 (17.6)

Table 1Characteristics of Pregnancy-Related Total Cardiovascular Conditions, Cardiomyopathy, and Other Cardiovascular Conditions Deathsa	**Total Cardiovascular Conditions (N = 210)**	**Cardiomyopathy (n = 84)**	**Other Cardiovascular Conditions (n = 126)**
30-34	61 (29.2)	19 (22.6)	42 (33.6)
35-39	54 (25.8)	22 (26.2)	32 (25.6)
40-44	15 (7.2)	7 (8.3)	8 (6.4)
45+	3 (1.4)	1 (1.2)	2 (1.6)
Missing	1	0	1
Education level			
12th grade or less; no diploma	34 (16.6)	11 (13.6)	23 (18.5)
High school grade or GED	89 (43.4)	34 (42.0)	55 (44.4)
Some college credit; no degree	38 (18.5)	17 (21.0)	21 (16.9)
Associate or bachelor's degree	34 (16.6)	15 (18.5)	19 (15.3)
Advanced degree	10 (4.9)	4 (4.9)	6 (4.8)
Missing	5	3	2
Was there an autopsy?			
Yes	120 (58.3)	43 (51.8)	77 (62.6)

Table 1Characteristics of Pregnancy-Related Total Cardiovascular Conditions, Cardiomyopathy, and Other Cardiovascular Conditions Deathsa	**Total Cardiovascular Conditions (N = 210)**	**Cardiomyopathy (n = 84)**	**Other Cardiovascular Conditions (n = 126)**
Report available	120	43	77
Report not available	0	0	0
No	86 (41.8)	40 (48.2)	46 (37.4)
Missing	4	1	3

Values are n (%).

AI/AN = American Indian or Alaska Native; GED = general education diploma; NHOPI = Native Hawaiian or other Pacific Islander.

a Excludes hypertensive disorders of pregnancy and cerebrovascular accidents. Data with missing values are not included in the distribution percentages.

Pregnancy-related CV deaths with information on timing of death are presented overall and by CM and OCV in **Figure 1**. Among CV deaths overall, two-thirds (67%) occurred from 7 days to 1 year following the end of pregnancy, including 40% who died from 43 days to 1 year after the end of pregnancy. Among the pregnancy-related CM deaths, over half (53%) occurred 43 days to 1 year after the end of pregnancy, while 12% occurred during pregnancy. Among pregnancy-related OCV deaths, 31% occurred 43 days to 1 year after the end of pregnancy, while 25% occurred during pregnancy.

Timing of Preventable Pregnancy-Related Cardiovascular Deaths

Timing of death was missing or unknown for 1 pregnancy-related cardiomyopathy death. The figure shows the percentage of pregnancy-related deaths with an MMRC-identified underlying cause of death of cardiovascular conditions (excluding hypertensive disorders of pregnancy and cerebrovascular accidents) at 5 time periods from pregnancy to 1-year postpartum. The percentages are displayed for total cardiovascular conditions, and then for cardiomyopathy and other cardiovascular conditions individually. Percentages might not sum to 100 because of rounding. MMRC = Maternal Mortality Review Committee.

The distribution of the specific CV-related MMRC-identified underlying cause of death subcategories is presented in **Table 2**. More than half (56.0%) of all pregnancy-related CM deaths were attributed to postpartum/peripartum CM, and 7.1% attributed to hypertrophic CM. Almost two-thirds (64.3%) of CM deaths among non-Hispanic Black persons were due to postpartum/peripartum CM, and 2.4% were due to hypertrophic CM (data not shown). In contrast, about half (51.5%) of the CM deaths among non-Hispanic White persons were due to postpartum/peripartum CM, and 9.1% were due to hypertrophic CM (data not shown). Among the pregnancy-related deaths due to OCV, the most frequent subcategories of cause of death were vascular aneurysm/dissection (19.8%), hypertensive cardiovascular disease (14.3%), coronary artery disease/myocardial infarction/atherosclerotic cardiovascular disease (11.1%), conduction defects/arrhythmias (11.1%), and valvular heart disease (8.7%) (**Table 2**).

Table 2Specific Cause of Death Subcategories Among Cardiomyopathy and Other Cardiovascular Conditions Pregnancy-Related Deathsa	**Cardiomyopathy (n = 84)**	**Other Cardiovascular Conditions (n = 126)**
Postpartum/peripartum	47 (56.0)	- (–)

Table 2Specific Cause of Death Subcategories Among Cardiomyopathy and Other Cardiovascular Conditions Pregnancy-Related Deathsa	**Cardiomyopathy (n = 84)**	**Other Cardiovascular Conditions (n = 126)**
cardiomyopathy		
Hypertrophic cardiomyopathy	6 (7.1)	- (–)
Other cardiomyopathy/NOS	31 (36.9)	- (–)
Coronary artery disease/myocardial infarction/atherosclerotic cardiovascular disease	- (–)	14 (11.1)
Pulmonary hypertension	- (–)	6 (4.8)
Valvular heart disease	- (–)	11 (8.7)
Vascular aneurysm/dissection	- (–)	25 (19.8)
Hypertensive cardiovascular disease	- (–)	18 (14.3)
Marfan syndrome	- (–)	2 (1.6)
Conduction defects/arrhythmias	- (–)	14 (11.1)
Vascular malformations outside head and coronary arteries	- (–)	1 (0.8)
Cardiovascular/NOS, including congestive heart failure, cardiomegaly, cardiac hypertrophy, cardiac fibrosis, nonacute myocarditis	- (–)	35 (27.8)

Values are n (%).

NOS = not otherwise specified.

a Excludes hypertensive disorders of pregnancy and cerebrovascular accidents.

A preventability determination was made by the MMRCs for 97.6% of pregnancy-related CV deaths. Overall, 76.1% of CV deaths were determined to be preventable, with 77.1% of CM and 75.4% of OCV deaths identified by MMRCs as having at least some chance of prevention (**Table 3**).

Table 3Preventability and Circumstances Surrounding Death Among Total Cardiovascular Conditions, Cardiomyopathy, and Other Cardiovascular Conditions Deathsa	**Total Cardiovascular Conditions (N = 210)**	**Cardiomyopathy (n = 84)**	**Other Cardiovascular Conditions (n = 126)**
Was the death preventable?			
Yes	156 (76.1)	64 (77.1)	92 (75.4)
No	49 (23.9)	19 (22.9)	30 (24.6)
Missing or unable to determine	5	1	4
Was obesity a circumstance of the death?			
Yes	68 (32.4)	28 (33.3)	40 (31.7)
Probably	29 (13.8)	12 (14.3)	17 (13.5)
No	105 (50.0)	39 (46.4)	66 (52.4)

Table 3Preventability and Circumstances Surrounding Death Among Total Cardiovascular Conditions, Cardiomyopathy, and Other Cardiovascular Conditions Deathsa	**Total Cardiovascular Conditions (N = 210)**	**Cardiomyopathy (n = 84)**	**Other Cardiovascular Conditions (n = 126)**
Unknown	8 (3.8)	5 (6.0)	3 (2.4)
Was substance use disorder a circumstance of the death?			
Yes	23 (11.1)	14 (16.7)	9 (7.3)
Probably	11 (5.3)	3 (3.6)	8 (6.5)
No	160 (76.9)	59 (70.2)	101 (81.5)
Unknown	14 (6.7)	8 (9.5)	6 (4.8)
Missing	2		2
Were mental health conditions a circumstance of the death?			
Yes	17 (8.2)	6 (7.1)	11 (8.9)
Probably	14 (6.7)	6 (7.1)	8 (6.5)
No	158 (76.0)	63 (75.0)	95 (76.6)
Unknown	19 (9.1)	9 (10.7)	10 (8.1)

Table 3Preventability and Circumstances Surrounding Death Among Total Cardiovascular Conditions, Cardiomyopathy, and Other Cardiovascular Conditions Deathsa	**Total Cardiovascular Conditions (N = 210)**	**Cardiomyopathy (n = 84)**	**Other Cardiovascular Conditions (n = 126)**
Missing	2		2
Was discrimination a circumstance of the death?			
Yes	14 (12.2)	5 (12.5)	9 (12.0)
Probably	17 (14.8)	5 (12.5)	12 (16.0)
No	51 (44.3)	15 (37.5)	36 (48.0)
Unknown	33 (28.7)	15 (37.5)	18 (24.0)
Missing	11	7	4

Values are n (%). Circumstances are defined as whether the condition/circumstance contributed to the death, and not just whether it was present.

Discrimination assessed among 126 pregnancy-related deaths (CM = 47, OCV = 79) reviewed after this question was added to MMRIA on May 29, 2020.

Data missing values are not included in the distribution percentages.

a Excludes hypertensive disorders of pregnancy and cerebrovascular accidents.

MMRC determinations of circumstances surrounding CV deaths are shown in **Table 3**. MMRCs identified that obesity was a circumstance (yes or probably) in almost half of CM deaths (47.6%) and OCV deaths (45.2%). There were 115 pregnancy-related CV deaths reviewed on or after May 29, 2020, which included an MMRC determination for whether discrimination was a circumstance of the death. MMRCs identified that discrimination was a circumstance (yes or probably) in 25.0% of the CM deaths and 28.0% of the OCV deaths (**Table 3**).

A total of 944 contributing factor classes were reported by MMRCs, for a mean of approximately 6 contributing factor classes for each preventable pregnancy-related CV death (**Table 4**). The most commonly identified contributing factor classes were Knowledge (n = 115, 12.2%), Clinical Skill/Quality of Care (n = 111, 11.8%), Continuity of Care/Care Coordination (n = 103, 10.9%), Chronic Disease (n = 79, 8.4%), and Access/Financial (n = 64, 6.8%). These 5 contributing factor classes accounted for 50% of the total identified by MMRCs.

Table 4Contributing Factor Classes Among Preventable Pregnancy-Related Total Cardiovascular Conditions, Cardiomyopathy, and Other Cardiovascular Conditions Deathsa	**Total Cardiovascular Conditions (N = 944)**	**Cardiomyopathy (n = 402)**	**Other Cardiovascular Conditions (n = 542)**
Knowledge	115 (12.2	62 (15.4	53 (9.8)
Clinical Skill/Quality of Care	111 (11.8)	47 (11.7)	64 (11.8)

Table 4Contributing Factor Classes Among Preventable Pregnancy-Related Total Cardiovascular Conditions, Cardiomyopathy, and Other Cardiovascular Conditions Deathsa	**Total Cardiovascular Conditions (N = 944)**	**Cardiomyopathy (n = 402)**	**Other Cardiovascular Conditions (n = 542)**
Continuity of Care/Care Coordination	103 (10.9)	33 (8.2)	70 (12.9)
Chronic Disease	79 (8.4)	28 (7.0)	51 (9.4)
Access/Financial	64 (6.8)	25 (6.2)	39 (7.2)
Assessment	56 (5.9)	13 (3.2)	43 (7.9)
Delay	56 (5.9)	30 (7.5)	26 (4.8)
Communication	48 (5.1)	26 (6.5)	22 (4.1)
Adherence	45 (4.8)	18 (4.5)	27 (5.0)
Policies/procedures	42 (4.5)	17 (4.2)	25 (4.6)
Substance use disorder	37 (3.9)	14 (3.5)	23 (4.2)
Discrimination	35 (3.7)	12 (3.0)	23 (4.2)
Referral	33 (3.5)	17 (4.2)	16 (3.0)
Social support/isolation	23 (2.4)	13 (3.2)	10 (1.8)
Other	18 (1.9)	8 (2.0)	10 (1.8)
Tobacco use	14 (1.5)	5 (1.2)	9 (1.7)
Mental health conditions	13 (1.4)	8 (2.0)	5 (0.9)
Outreach	12 (1.3)	7 (1.7)	5 (0.9)
Structural racism	10 (1.1)	4 (1.0)	6 (1.1)

Table 4Contributing Factor Classes Among Preventable Pregnancy-Related Total Cardiovascular Conditions, Cardiomyopathy, and Other Cardiovascular Conditions Deathsa	Total Cardiovascular Conditions (N = 944)	Cardiomyopathy (n = 402)	Other Cardiovascular Conditions (n = 542)
Cultural/religious	7 (0.7)	3 (0.7)	4 (0.7)
Equipment/technology	6 (0.6)	5 (1.2)	1 (0.2)
Violence	5 (0.5)	3 (0.7)	2 (0.4)
Environmental	4 (0.4)	1 (0.2)	3 (0.6)
Unstable housing	3 (0.3)	2 (0.5)	1 (0.2)
Interpersonal racism	2 (0.2)	0 (0.0)	2 (0.4)
Legal	1 (0.1)	0 (0.0)	1 (0.2)
Personnel	1 (0.1)	0 (0.0)	1 (0.2)
Trauma	1 (0.1)	1 (0.2	0 (0.0)

Values are n (%). Complete list of all 27 specific contributing factor classes, and “other”, available for selection by Maternal Mortality Review Committees. 1 preventable pregnancy-related death had no contributing factor classes specified.

a Excludes hypertensive disorders of pregnancy and cerebrovascular accidents.

Example MMRC recommendations

Example MMRC recommendations within the 5 most frequent contributing factor classes are listed in **Table 5**. Knowledge was the most frequent contributing factor class. Example recommendations that address Knowledge included: “community-based organizations should develop public education campaigns to raise awareness of warnings signs of early postpartum complications, when to seek care, and emphasize 1-year

postpartum as critical window"; and “Care Coordination or Navigators at the managed care organization level and community support services to assess where patient is at, what they understand, and any needs they have” (**Table 5**).

Table 5Example MMRC Recommendations Addressing Most Frequent Contributing Factor Classes Among Preventable Pregnancy-Related Cardiovascular Conditions Deathsa,b **Contributing Factor Class**	**Example MMRC Recommendations**
Knowledge	Community-based organizations should develop public education campaigns to raise awareness of warnings signs of early postpartum complications, explain when to seek care, and emphasize 1-y postpartum as critical window.
	Providers should assure that there are appropriate instructions, given at the time of discharge, for when to call with problems.
	Providers who treat pregnant and postpartum women should adhere to evidence-based guidelines and practices to support high-quality care of maternal hypertension and should ensure appropriate consultation and referral practices.

Table 5Example MMRC Recommendations Addressing Most Frequent Contributing Factor Classes Among Preventable Pregnancy-Related Cardiovascular Conditions Deathsa,b **Contributing Factor Class**	**Example MMRC Recommendations**
	All delivering facilities should provide education regarding postpartum warning signs prior to discharge.
	Care Coordination or Navigators at the managed care organization level and community support services to assess: where patient is at, what they understand, and any needs they have. Universal access to community health workers for all expectant families.
Clinical Skill/Quality of Care	All providers should educate themselves regarding the American College of Obstetricians and Gynecologists (ACOG) guidelines for screening for cardiovascular disease in pregnancy.
	Providers and managed care organizations should ensure that their patients (members) with prior cardiac history have consultation with cardiologist (preconception, prenatally, and postpartum) and that there are

Table 5Example MMRC Recommendations Addressing Most Frequent Contributing Factor Classes Among Preventable Pregnancy-Related Cardiovascular Conditions Deathsa,b **Contributing Factor Class**	**Example MMRC Recommendations**
	processes in place to ensure coordination of care and information sharing as soon as possible.
	Facilities and providers should complete comprehensive postpartum discharge planning for high-risk pregnancies/deliveries in alignment with ACOG Committee Opinion #736: Optimizing Postpartum Care.
	Hospital emergency departments should have policies for identifying pregnancy/postpartum status for all women who present for care.
	Professional societies should provide education to providers on signs and symptoms of aortic dissection.
	ACOG and partners should develop an emergency room bundle for the care of pregnant women.
Continuity of Care/Care Coordination	Patients should be able to have access to continued care with one provider house (care umbrella with one

Table 5Example MMRC Recommendations Addressing Most Frequent Contributing Factor Classes Among Preventable Pregnancy-Related Cardiovascular Conditions Deathsa,b **Contributing Factor Class**	**Example MMRC Recommendations**
	provider/clinic in the lead) throughout the course of a person's illness/care.
	A patient who is identified as high risk needs a care coordinator who is following her individually, throughout the course of care, to assure she goes back to the same care provider each time and helps her navigate information and the system. This person would also coordinate the patient's appointments, help her with mental health referrals, and encourage compliance with medical recommendations.
	Hospitals should assign designated care coordinators to patients requiring multidisciplinary care at first contact with health care system after emergency department visit.
	Facilities should have a system to follow-up with patients discharged after preeclampsia/hemorrhage

Table 5Example MMRC Recommendations Addressing Most Frequent Contributing Factor Classes Among Preventable Pregnancy-Related Cardiovascular Conditions Deathsa,b **Contributing Factor Class**	**Example MMRC Recommendations**
	diagnoses and make sure patients see follow-up providers, including cardiology.
	Hospital systems should have patient-centered, multidisciplinary, coordinated care (with use of bundles) as part of discharge planning for patients with chronic illnesses, especially during the postpartum period.
	Advocate for system integration for inpatient-to-outpatient transitions and specialist-to-primary care transitions.
Chronic Disease	Providers should refer all patients with history of complex medical issues to case management services during the first prenatal visit and throughout the pregnancy and postpartum.
	Providers should provide reproductive life planning/interconception care/family planning counseling to women with chronic conditions.

Table 5Example MMRC Recommendations Addressing Most Frequent Contributing Factor Classes Among Preventable Pregnancy-Related Cardiovascular Conditions Deathsa,b **Contributing Factor Class**	**Example MMRC Recommendations**
	Providers should educate women on the importance of preconception health, especially in the context of chronic disease and/or obesity.
	Obstetric providers should refer patients with reported cardiac conditions to a cardiologist during pregnancy and postpartum.
	Facilities and payers should provide case management services to women with chronic health conditions during pregnancy and postpartum.
	Community-based organizations should educate women on the importance of preconception health, especially in the context of chronic disease and/or obesity.
Access/Financial	Hospitals should employ a social worker or case manager who can conduct and document a psychosocial needs assessment prior to delivery hospital discharge—to identify

Table 5Example MMRC Recommendations Addressing Most Frequent Contributing Factor Classes Among Preventable Pregnancy-Related Cardiovascular Conditions Deathsa,b **Contributing Factor Class**	**Example MMRC Recommendations**
	potential barriers to care and connect women to resources and postpartum case management.
	Insurers should provide navigation services to individuals with transportation barriers—to use transportation as a covered benefit.
	Medicaid should improve the application process to make it user friendly and more easily accessible.
	Medicaid should streamline enrollment to support early and easy entry into prenatal care (including specialty care).
	Medicaid should be extended to 1 year for all postpartum women, particularly for those with hypertensive disorders of pregnancy; and enrollment and maintenance processes should be streamlined.

MMRC = Maternal Mortality Review Committee.

a Maternal Mortality Review Committee recommendations were edited slightly for clarity.

b Excludes hypertensive disorders of pregnancy and cerebrovascular accidents.

Clinical Skill/Quality of Care was the second most frequent contributing factor class. Examples of MMRC recommendations addressing this class included: “providers and managed care organizations should ensure that their patients and members have consultation with cardiologist for people (preconception, prenatally, and postpartum) with prior cardiac history and that there are processes in place to ensure coordination of care and information sharing as soon as possible”; and “professional societies should provide education to providers on signs and symptoms of aortic dissection” (**Table 5**).

Continuity of Care/Care Coordination was third most frequent contributing factor class. Examples of MMRC recommendations that address this contributing factor included: “patient who is identified as high risk needs a care coordinator who is following her individually, throughout the course of care, to assure she goes back to the same care provider each time and helps her to navigate information and the system. This person would also coordinate her appointments, help her with mental health referrals, and encourage compliance with medical recommendations”; and “advocate for system integration for inpatient to outpatient and specialist to primary care” (**Table 5**).

Chronic Disease was fourth most frequent contributing factor class. Examples of MMRC recommendations that address Chronic Disease included examples such as: “community-based organizations should educate women on the importance of preconception and interconception health, especially in the context of chronic disease and/or obesity”; and “facilities and payers should provide case management services to women with chronic health conditions during pregnancy and postpartum” (**Table 5**).

Access/Financial was the fifth most frequent contributing factor class. Examples of MMRC recommendations that address these contributing

factors include “hospitals should employ a social worker or case manager who can conduct and document a psychosocial needs assessment prior to delivery hospital discharge to identify potential barriers to care and connect women to resources and postpartum case management”; and “Medicaid should improve the application process to make it user friendly and more easily accessible” (**Table 5**).

Discussion

MMRCs determined that 76% of CV deaths were preventable. The most common contributing factor classes were Knowledge, Clinical Skill/Quality of Care, and Continuity of Care/Care Coordination (**Central Illustration**). The detailed multidisciplinary MMRC reviews, based on the context of their state, position committees to develop specific and actionable recommendations. The breadth of the 5 most frequent contributing factors and the average number (6) associated with each pregnancy-related death are emblematic of the complexity of pregnancy-related mortality. The social ecological model provides a framework for considering the complex interplay among multilevel contexts.**6** Committees consider not only the health care and clinical events near the time of death; they also can include the broader context using tools to understand the social and built environments, neighborhood resources, and structural inequality.**7** The social ecological model stresses that these multiple contexts are interrelated, highlighting the importance of addressing multiple dimensions simultaneously to improve health outcomes.**6**

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Central Illustration

Cardiomyopathy and Other Cardiovascular Conditions Are Among the Most Frequent Causes of Pregnancy-Related Death in the United States

We analyzed pregnancy-related death data from MMRCs in 32 states, occurring during 2017 to 2019, with MMRC-determined underlying causes

of cardiovascular conditions. Over 75% of pregnancy-related deaths were determined by MMRCs to be preventable. The five most common contributing factor classes were knowledge, clinical skill/quality of care, continuity of care/care coordination, chronic disease, access/financial. Example MMRC recommendations illustrate prevention opportunities that address contributing factors, including broader awareness of urgent warning signs, improved handoffs for care coordination and continuity, and expanded accessibility of community-based comprehensive and integrated care services. Abbreviation as in **Figure 1**.

Knowledge was the most commonly identified contributing factor class among CV deaths. Example MMRC recommendations, intended to prevent future deaths from this contributing factor class, included increasing knowledge about urgent maternal warning signs. CDC's Division of Reproductive Health's *Hear Her* campaign seeks to raise awareness of urgent maternal warning signs during and after pregnancy and improve communication between patients and their health care providers.**8** Both patient-facing and provider-facing materials are available. Health system support for this awareness can include facility-based programs that educate nurses and other health care professionals about the timeline for postpartum risk and the significance of postpartum maternal mortality.**9**

Over half (53%) of CM deaths and almost one-third (31%) of deaths from OCV occurred in the late postpartum period (43 days to 1 year after the end of pregnancy). The timing of these deaths emphasizes the need for tailored postpartum care and a multidisciplinary approach. The creation and use of comprehensive postpartum plans—with careful consideration of each patient's risk profile and access to resources—has been proposed to facilitate effective handoffs needed in the first few days to months after pregnancy ends.**10**,**11** The American College of Obstetricians and Gynecologists (ACOG) recommends a postpartum follow-up visit with either the primary care provider or cardiologist within 7 to 14 days of delivery for women with heart disease/cardiovascular disorders.**12** Individuals identified as high risk should be evaluated at 3 months in a comprehensive

cardiovascular postpartum visit with a Pregnancy Heart Team or cardio-obstetrics team, obstetrician-gynecologist, or other primary care provider.**11**,**12** Women with cardiovascular risk factors or new-onset CV may be unable to access ongoing treatment because of gaps in health care coverage in the postpartum period.**13**,**14**

Example MMRC recommendations related to the contributing factor class of Access/Financial include extension of Medicaid for 12 months postpartum along with simplification of the enrollment and maintenance process for Medicaid. As of February 2024, 45 states have implemented a 12-month postpartum extension of Medicaid.**15** In addition, Medicaid reforms to reduce burdens to care—including continuous eligibility, presumptive eligibility, and coordinated care services—may enable more consistent access to care, including prenatal care.**16**

Example MMRC recommendations related to the contributing factor class of Continuity of Care/Care Coordination identified the need to address gaps in care coordination and transition of care between prenatal care, specialty care, hospitalization, postpartum care, and ongoing health maintenance. Integrated patient care includes coordination of care both within and across teams and with the community, along with patient-centeredness and shared responsibility.**17** A recent systematic review of care coordination programs in pregnancy noted that “although the components of the care coordination programs included (in the analysis) suggest only a modest improvement in fetal outcomes, the benefits to the participants—both patients and providers—may extend beyond the brief course of the pregnancy.”**18** Additional research, to evaluate the impact of integrated care in pregnancies with complications on broader, long-term outcomes, could be beneficial.

Example MMRC recommendations related to the contributing factor class of Clinical Skills included screening, risk identification, and consultation or referral of people identified as high risk. Screening algorithms have been recommended by ACOG**12** and others,**19**,**20** and screening for CV

conditions in pregnancy has been recommended as a quality measure.**21** Consultation with or referral to a cardio-obstetrics team (also known as Pregnancy Heart Team) for risk stratification and multidisciplinary care is recommended**12**,**22** because late pregnancy assessment has been associated with frequent adverse cardiac complications during pregnancy.**2**,**23** Multidisciplinary meetings of the cardio-obstetrics team facilitate patient-centered coordination of planning antenatal, delivery, and postpartum care.**12**,**22**

Example MMRC recommendations related to the contributing factor class of Chronic Disease include the role of preconception health optimization. Recent studies have evaluated the prevalence of cardiovascular risk factors (including hypertension, diabetes, obesity, and tobacco use) among persons of reproductive age (age 20-44 years).**24-26** Prevalence rates for hypertension and diabetes were higher among non-Hispanic Black individuals than Hispanic or non-Hispanic White individuals.**25**,**26** The importance of preconception health is consistent with the need to move upstream to address the prevalence of these conditions and address the gap in cardiovascular disease prevention in younger adults.**27**

Two-thirds (66%) of the pregnancy-related deaths due to CV occurred among people under the age of 35 years, as did the majority of all pregnancy-related deaths and the majority of births.**3** Women aged 18 to 55 years are 50% more likely than similar aged men to present without chest pain when they have ST-segment elevation myocardial infarction, with 1 in 5 women perceiving their symptoms as related to anxiety or stress vs acute myocardial infarction.**28-30** Spontaneous coronary artery dissection causes more than 40% of myocardial infarctions in pregnancy and the postpartum period.**30** spontaneous coronary artery dissection, which has been clinically underrecognized, occurs predominantly in young women (mean age 40-42 years) with few or no conventional risk factors for atherosclerosis.**31**,**32**

Vascular aneurysms/dissections accounted for 19.8% of the deaths due to OCV. A recent analysis of aortic dissection during pregnancy identified

Marfan syndrome, primary hypertension, and preeclampsia/eclampsia as significantly associated with the risk of aortic dissection during pregnancy and the puerperium.**33** There is a growing need to identify high-risk patients and provide them with aggressive prevention and monitoring.**33-35** Efforts at the health system level are required to increase assess to perinatal care because earlier interventions may result in more favorable outcomes.**33** Prompt diagnosis and therapy are noted by some to be the only factors critical to acute aortic dissection survival.**35**

Example MMRC recommendations for the contributing factor class of Clinical Skill/Quality of Care noted the need for education to enhance recognition and management of these CV conditions among clinicians, including those in emergency medicine and obstetrician-gynecologists. In response to MMRC findings and recommendations for enhanced emergency care, ACOG recently developed and released resources to help practitioners in nonobstetric settings identify and manage pregnancy-related emergencies, including cardiovascular disease in pregnancy and postpartum.**36**

The strengths of our analysis include the detailed data available from MMRCs in 32 states. The committees in these states use a broad array of data sources and multidisciplinary memberships to provide a deeper understanding of pregnancy-related mortality—recognizing medical and nonmedical contributors to deaths. The identified contributing factor classes and example MMRC recommendations highlight options to prioritize interventions for reducing pregnancy-related deaths due to CV conditions.

Study limitations

Despite the strengths of this multistate analysis, there are limitations. The data are aggregated from individual state-based review committees. While MMRCs utilize a standardized review process, variations in review may have existed. MMRIA data are based on the availability and completeness of abstracted data. Not every state contributed data, and partial years of death were included; thus, findings are not representative of all pregnancy-related

CV deaths nor does this represent a population-based census of pregnancy-related deaths due to CV. Cause-specific pregnancy-related mortality ratios cannot be calculated. While most CM deaths were attributed to postpartum and peripartum CM, a large percentage were classified as other CM/NOS. Similarly, a significant proportion of the deaths due to OCV were categorized as other/NOS and may belong in a more specific condition category. The contributing factor classes of discrimination, interpersonal racism, and structural racism were not added to the MMRIA Committee Decisions Form until May 2020 and would not have been considered in the MMRC review of all pregnancy-related deaths in this analysis. Therefore, these classes may have contributed to pregnancy-related deaths more frequently than reported in this analysis. We present example MMRC recommendations among only the 5 most frequently occurring contributing factor classes; thus, this does not represent the full spectrum of the MMRC-identified prevention opportunities. Despite these limitations, this study adds to our understanding of CV as a major contributor to pregnancy-related mortality.

Conclusions

Most pregnancy-related deaths due to CV are preventable, and recommendations for preventing future deaths and improving maternal outcomes require interventions across multiple contexts. Jurisdiction-based MMRCs evaluate and interpret comprehensive data and provide information on specific contributing factor classes and recommendations in the local context. Common contributing factor classes and example MMRC recommendations provided in this report illustrate the breadth of prevention opportunities—such as broader awareness of urgent warning signs, improved handoffs for care coordination and continuity, and expanded accessibility of community-based comprehensive and integrated care services.

10. Gestational Diabetes and Future CVD

Study Questions:

What is the causality between genetic predisposition to gestational diabetes mellitus (GDM) and the risk of cardiovascular disease (CVD)?

Methods:

This study applied Mendelian randomization analyses to data from the FinnGen consortium, UK Biobank consortium, and/or genome-wide association meta-analysis studies.

Results:

In Mendelian randomization analyses, genetic predisposition to GDM was associated with increased risk of coronary artery disease (odds ratio, 1.09 [95% confidence interval, 1.01-1.17] per unit increase in the log-odds of genetic predisposition to GDM in ever-pregnant women). Type 2 diabetes and hypertension were causal mediators.

Conclusions:

Interval development of type 2 diabetes and hypertension mediated the casual relationship between GDM and future CVD.

Perspective:

Prior observational studies have indicated that patients with GDM are at higher risk for subsequent CVD. The authors sought to determine the causality by linking genetic predisposition for GDM with future CVD. Interestingly, the association was mainly mediated by the interval development of type 2 diabetes and hypertension, which are well-recognized cardiometabolic risk factors for CVD.

This study population was of European ancestry and future studies in populations with racial and ethnic diversity would be useful. Additionally, this study identified type 2 diabetes and hypertension as causal mediators, but other mediators such as socioeconomic and lifestyle factors were not studied. Granular data such as blood pressure measurements, exercise capacity, lipid profiles, and body mass index were also not available but could be useful in future studies.

Overall, the risk of CVD appears to be mediated by the interval development of type 2 diabetes and hypertension; therefore, ongoing careful management for primary prevention of CVD is important.

11. Risk of MI After Pregnancy With Hypertension

Study Questions:

What is the anatomy of coronary arteries and the type of coronary artery lesions in women with a history of hypertensive disorders of pregnancy (HDP)?

Methods:

This study used a population-based cohort of parous female patients with incident coronary artery disease (CAD) who underwent coronary angiography and age-matched control subjects. The SYNTAX (Synergy between PCI [percutaneous coronary intervention] with TAXUS [Boston Scientific] and Cardiac Surgery) score was assessed to determine the complexity and degree of CAD; myocardial infarction with nonobstructive coronary arteries (MINOCA) was diagnosed in the presence of clinical acute myocardial infarction (MI) in the absence of obstructive coronary disease. Acute coronary syndrome (ACS) was defined as patients with MI or those with PCI or coronary artery bypass grafting with ST-segment elevation MI, non–ST-segment elevation MI, or unstable angina, on clinical chart review. Multivariable models were adjusted for the following risk factors for CAD

unless otherwise specified: age, body mass index, smoking history, hyperlipidemia, diabetes, and hypertension.

Results:

A total of 506 parous female Olmsted County, Minnesota (USA) residents had incident CAD and angiographic data from November 7, 2002–December 31, 2016. Women with HDP were younger than normotensive women at the time of the event (median: 64.8 years vs. 71.8 years; p = 0.030). There was a strong association between HDP and ACS (unadjusted p = 0.018). In unadjusted models, the odds of overall HDP were significantly higher in ACS cases compared with control subjects (odds ratio [OR], 1.48; 95% confidence interval [CI], 1.07-2.05; p = 0.018), and results remained significant after independent adjustment of covariates. Women with HDP compared with women with normotensive pregnancies were more likely to have a higher SYNTAX score (OR, 2.28; 95% CI, 1.02-5.12; p = 0.046) and MINOCA (OR, 2.08; 95% CI, 1.02-4.25; p = 0.044).

Conclusions:

The present study reports several novel findings regarding HDP and the future risk for CAD by using a population-based cohort. First, women with a history of HDP on average experience CAD events 7 years earlier than women with a history of normotensive pregnancies. Second, there is a strong association between HDP and ACS that remained significant after controlling for demographic variables and comorbidities. Third, among ACS cases, women with a history of HDP compared with women with normotensive pregnancies were more likely to have a higher atherosclerotic burden, as demonstrated by the SYNTAX score, and a diagnosis of MINOCA.

Perspective:

Given the substantial evidence, a history of HDP is included as a nontraditional, sex-specific cardiovascular disease (CVD) risk factor in recent guidelines. Such inclusion is important because the increased risk in

women cannot be fully accounted for by the prevalence of traditional risk factors. Whether HDP facilitate subsequent CVD because of shared traditional risk factors and pathophysiological pathways or whether distinct mechanisms independent of conventional risk factors are playing a role is essentially unaddressed in the literature. These data demonstrate that nonatherosclerotic disease could play a significant role in the origin of ACS in 18% (i.e., one in five) of women with a history of HDP.

In this study, although most women with ACS and a history of HDP had clear evidence of MINOCA, one-third developed MI because of medical conditions leading to a mismatch in myocardial oxygen supply and demand, as in type 2 MI. Although the exact pathophysiology by which HDP promote ACS remains to be determined, recognition of a history of HDP as an independent risk factor for ACS, particularly MINOCA, may help stratify women who would benefit from risk reduction strategies and provide a novel therapeutic target for improving prognosis in women with ACS.

12. Risk of MI After Pregnancy With Hypertension

Study Questions:

What is the anatomy of coronary arteries and the type of coronary artery lesions in women with a history of hypertensive disorders of pregnancy (HDP)?

Methods:

This study used a population-based cohort of parous female patients with incident coronary artery disease (CAD) who underwent coronary angiography and age-matched control subjects. The SYNTAX (Synergy between PCI [percutaneous coronary intervention] with TAXUS [Boston Scientific] and Cardiac Surgery) score was assessed to determine the complexity and degree of CAD; myocardial infarction with nonobstructive coronary arteries (MINOCA) was diagnosed in the presence of clinical acute myocardial infarction (MI) in the absence of obstructive coronary disease. Acute coronary syndrome (ACS) was defined as patients with MI or those

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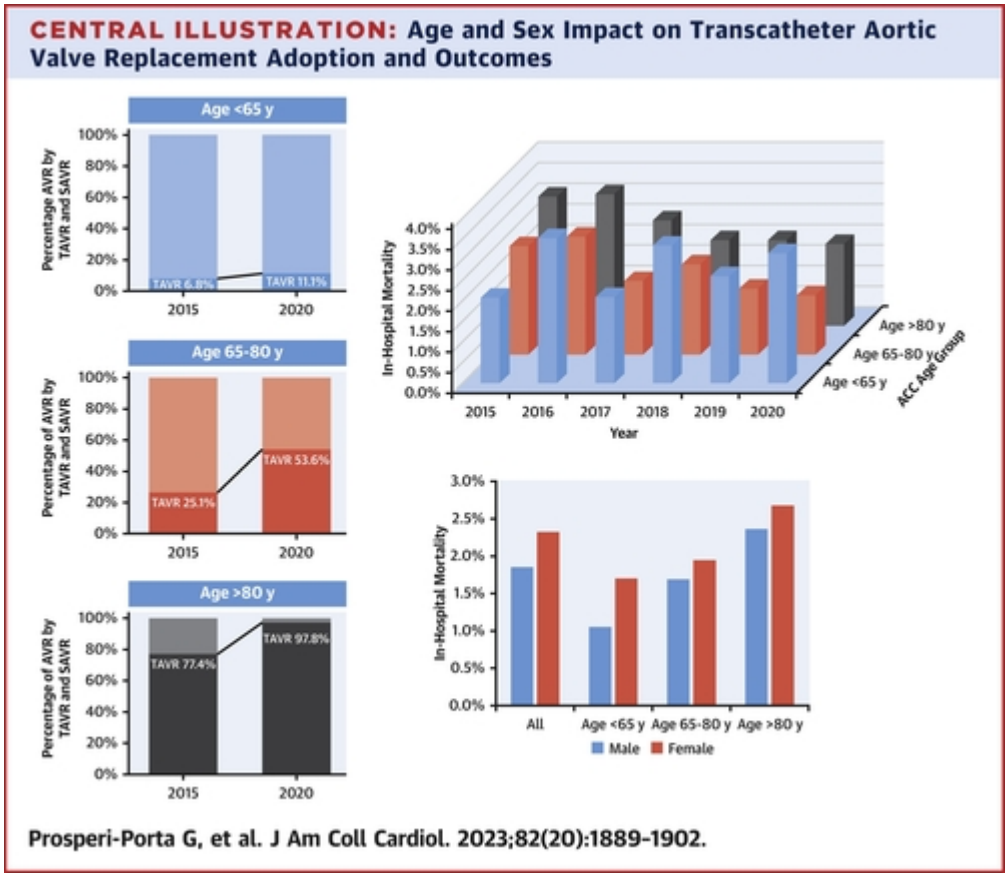


13. Risk Factors and Prevention Strategies for Gestational Diabetes in Asian Populations

Introduction

Gestational diabetes mellitus (GDM) affects 14% of pregnant women worldwide and is rising.**1** Uncontrolled high blood sugar levels during pregnancy can cause miscarriage, high blood pressure, low newborn blood sugar, and neonatal respiratory distress.**2** A history of GDM increases the risk of abnormal glucose metabolism, diabetes, and cardiovascular disease for both mother and child.**3**,**4** The difference in race and ethnicity affects GDM risk in addition to well-known risk factors like advanced maternal age, familial diabetes history, previous GDM, obesity, and hypertension.**5**,**6**

Several studies show that Asians have the highest GDM rates. A 1995-2004 study in California found that Asian Indians had 11.1% age-adjusted GDM prevalence, whereas non-Hispanic whites had 4.1%.**7** Another U.S. study found that Asian Indians had the highest GDM rates at 129.1 per 1,000 live

births from 2011-2019.**8** Despite the high risk of GDM in Asians, little was known about its causes. Thus, studies are needed to determine if age, weight, hypertension, or other factors are involved.

In this issue of *JACC: Asia*, Boyer et al**9** examined U.S. singleton pregnancies from 2016-2019 and the relationship between hypertension, obesity, and GDM by maternal race, ethnicity, nativity, and Asian ancestry. Asian Americans' GDM prevalence was 12.3%, the highest of any race or ethnicity. Japanese (7.3%), Korean (9.1%), and Chinese (10.9%) had the lowest prevalence among the Asian ancestries. These generally match that of previous research.**7**,**8** Asian Americans had the lowest rates of hypertension and obesity, but they had a much higher risk of GDM. The study found that GDM risk increased with prepregnancy body mass index (BMI), hypertension, maternal age, lower educational attainment, smoking, and delayed prenatal care. Most Asian Americans born outside the United States had a higher GDM risk than those born in the United States, possibly due to dietary habits, environmental factors, cultural differences, or social dynamics. These findings emphasize the importance of considering prepregnancy health and sociodemographic factors in preventing and managing GDM in U.S. Asian populations.

GDM risk in Asians may result from several factors. First, Asians have higher body fat, larger waist circumferences, and greater abdominal obesity than Europeans of similar BMI.**10**,**11** Asians may appear thin but store more visceral fat than Europeans, a condition called "skinny fat." High body fat and visceral fat can cause insulin resistance and type 2 diabetes mellitus (T2DM). Despite having lower BMIs, Asians are paradoxically more likely to develop GDM**7**,**8** and T2DM.**12** Future studies can test this hypothesis by incorporating waist circumference or abdominal visceral fat mass into investigation, which may be a better indicator of obesity than BMI, especially for cardiovascular health. The widespread use of BMI to assess health may lead to Asians underestimating their diabetes risk because many are lean with a low BMI, potentially delaying diagnosis. Second, studies have indicated that South Asians are more insulin-resistant and have lower β-cell

function than Whites.**13-16** East Asians, particularly the Japanese, are generally more insulin-sensitive than South Asians**13** and Whites.**17-19** This may explain why Boyer et al and previous studies found that the Japanese have a lower prevalence of GDM and T2DM than South Asians.**7-9** Third, Asian genetics may increase diabetes risk. In a genome-wide association meta-analysis, Loh et al**20** found 21 T2DM-related single nucleotide polymorphisms (SNPs) in South Asians and Europeans. A BMI-adjusted model was used to assess these SNPs in other ethnic groups. Of the 21 SNPs, 12 were replicated in East Asians, 1 in Africans, and none in Hispanics. These findings suggest that South Asians have T2DM-associated genetic loci that East Asians and other ethnic groups lack, which may explain the higher risk of GDM and T2DM in South Asians. Further genetic association research is needed to confirm these assumptions.

There are other behavioral factors that may affect diabetes risk in Asians. In this study, Boyer et al**9** found that most Asians born outside the United States have a higher GDM risk than those born in the United States, except the Japanese. Previous studies support this result.**7**,**21-23** Noah et al**21** found that foreign-born Asians were less educated, less insured, had more pregnancies, fewer chronic health conditions, and lower alcohol and cigarette use than U.S.-born Asians, and the risk difference between U.S.-born and non–U.S.-born women remained even after multivariable adjustment. Individuals who are foreign-born may be more disadvantaged in terms of economics and education, which may result in a higher risk of GDM due to limited medical resources, insurance coverage, or migration and environmental adaptation stress.**24** More investigation is required to elucidate these disparate presentations. The increased risk of GDM in foreign-born Asians is unlikely due to Asian diet, behavior, or lifestyle because previous studies have shown that GDM risk increases with U.S. residence.**21**,**25** Ogunwole et al**25** found that foreign-born women with ≥10 years of U.S. residency had the highest age-standardized GDM history (11.0%), followed by those with <10 years residency (6.7%) and U.S.-born women (9.2%). Noah et al**21** also found that foreign-born women living in

the United States for 0-5 years (8.3%), 6-10 years (14.0%), and >10 years (15.7%) had higher GDM rates than U. S.-born women. This suggests that foreign-born women living in the United States longer are more likely to develop GDM. In U.S. immigrants, longer residency was also associated with higher BMI and T2DM risk,**26**,**27** which may be attributed to the adoption of a Western diet and sedentary behavior. Lastly, as GDM is defined as glucose intolerance first recognized during pregnancy, only women without prepregnancy diabetes are at risk of developing GDM. A study conducted in Northern California revealed that the age-adjusted prevalence of prepregnancy T2DM from 2012-2014 was highest in Hispanics, second among African Americans, and third in Asians. Each of these prevalence estimates was significantly higher than that of non-Hispanic White women.**28** Thus, Asians may have a higher risk of GDM due to the exclusion of fewer prepregnancy T2DM patients compared to Hispanics and African Americans. This hypothesis needs confirmation from more research. Overall, besides cardiovascular risk factors, low educational and financial status, insufficient insurance coverage, limited access to medical care, stress related to migration adaptation, and potentially survivorship bias may contribute to the heightened risk of diabetes among Asians.

The study by Boyer et al**9** revealed several research gaps that could be addressed in future studies. The effects of central obesity (waist circumference), diet, exercise, and economic status on GDM risk were not assessed due to insufficient data. However, this study examined BMI, hypertension, ethnicity, country of birth, and Asian ancestry as potential GDM risk factors. This analysis offers valuable insights into the risk of GDM in the Asian population.

Asians are more likely to develop GDM, so active glucose monitoring during pregnancy is crucial. Asians at risk of GDM can be identified in several ways. The American College of Obstetricians and Gynecologists recommends screening at 24 weeks' gestation for women with BMI ≥25 kg/m2 or ≥23 kg/m2 in Asian Americans.**29** Due to insufficient evidence of maternal and neonatal benefits outweighing risks, they do not recommend screening

before 24 weeks. Future research should examine whether Asians could benefit from earlier screening. Given that Asians have lower BMI but higher body fat, future research should also explore whether waist circumference is better than BMI at identifying GDM risk in Asians. Additionally, more sensitive GDM diagnostic criteria may help identify Asian women at risk. Hirst et al**30** found that the less strict International Association of the Diabetes and Pregnancy Study Groups criterion identified more pregnant women at risk for GDM than the American Diabetes Association criterion. A high risk of preterm delivery and neonatal hypoglycemia was associated with those diagnosed with GDM using International Association of the Diabetes and Pregnancy Study Groups but tested negative using American Diabetes Association. More research is needed to determine if current diagnostic criteria can detect glucose intolerance in Asians and if a less strict approach could improve early management. However, whether healthcare resources can handle the increased number of GDM patients if such criteria are adopted should also be considered.

GDM screening during pregnancy and T2DM screening after GDM are essential for Asians. In a retrospective cohort study conducted by Janevic et al,**31** Africans (18.5%) had the highest 8-year incidence of T2DM among GDM patients, followed by South and Southeast Asians (16.8%). Therefore, establishing customized criteria for T2DM screening in Asians is crucial. Araneta et al**32** proposed that, while many guidelines are based on European and U.S. studies,**33** an HbA1c cutoff of ≥6.5% may be insensitive for Asian Americans and could delay their T2DM diagnosis. Asians with prediabetes should be treated more proactively, and further research should determine if current T2DM guidelines are suitable for them.

The prevalence of GDM is higher among Asians as a result of genetic factors and lifestyle choices. Boyer et al**9** offer valuable knowledge regarding the influence of prepregnancy health and sociodemographic factors on the likelihood of developing GDM in Asian populations. We provide various hypotheses to improve understanding of this pattern. We suggest

conducting additional research to identify and efficiently manage the high occurrence of diabetes among individuals of Asian descent.

14. Talking Sex: CVD Patients Want to Hear More From Clinicians

More than three-quarters of patients with cardiovascular disease have concerns related to sexual health and intimacy, but few report receiving information or counseling on those topics from their healthcare team, a survey from Sweden reveals.

When it comes to talking about sex in a clinical setting, “I saw that people struggle with it, and no one [brings] the subject up,” said Tiny Jaarsma, PhD (Linköping University, Sweden), lead author of the new study, which was presented as an abstract this past weekend at the American Heart Association (AHA) 2024 Scientific Sessions.

Overall, 76% of those who took the survey said their disease affected their sexual health as well as their mood and well-being. Compared with women, men were more likely to report an impact on their sexual health (65% vs 35%; P= 0.02) and mood/well-being (64% vs 36%; P < 0.01).

Fully 78% wanted to receive information on sexual health, but counter to this interest, only 5% received it. Men were more likely than women to say they wanted this information (87% vs 64%; P= 0.02).

“If [patients] ask about it, it’s fine. Nurses and cardiologists: they can talk about it. But nobody spontaneously will ask, ‘How about your intimate life or your sexual health?’ Or [say], ‘Now we’re uptitrating this medication. If you have any problems, it could be cold hands and feet or sexual problems. Please talk to me.’ Nobody does that,” Jaarsma told TCTMD. “What I saw in clinical practice is that a lot of patients struggle with the question and don’t really dare to ask.”

Jaarsma has long had an interest in these conversations—or the lack thereof—and seen evidence of a gap between what guidance patients want and what advice they get across a variety of countries, including the United States, the Netherlands, and now Sweden.

In Sweden, said Jaarsma, there's no formal means of communicating about sexual health with cardiovascular patients. Yet it's clear patients want this resource, even if it's just a pamphlet, so the researchers conducted their nationwide survey to gather data.

The Survey

Jaarsma et al reached out to patient organizations, clinical outpatient departments, and social media to survey 135 Swedish cardiac patients about their thoughts on sexual health. Mean age of the respondents was 65, and 59% were male. Nearly half (47%) had hypertension, 36% a history of MI, 30% atrial fibrillation, and 24% heart failure. The online survey consisted of 21 questions.

Specifically, the survey respondents most wanted to hear about side effects (60%), erectile dysfunction (50%), impact on relationships (47%), and anxiety before sex (35%). As might be expected, men were more keen to receive details on erectile dysfunction (80% vs 7% of women), but women were more likely to want to learn about pain during sex (13% vs 1% of men; $P < 0.01$ for both comparisons).

The most popular time for receiving such information would be during annual checkups (57%) and/or at the time of diagnosis (51%). While most people (79%) wanted to have an actual conversation with their healthcare professional, others wanted to receive the information over time from various sources (43%).

Based on their results, the researchers are now working with the Swedish Heart Lung Foundation to develop a brochure on the topic, Jaarsma said.

They wanted to have the foundation involved so that the end result is trusted as a reliable source.

“This study aligns with a small body of research indicating that feelings of shame and discomfort about sex—sexual health—can serve as obstacles to counseling patients about their heart health and resuming sex after heart disease,” Jennifer H. Mieres, MD (Northwell Health, Lake Success, NY), said in a commentary for the media provided by the AHA. “The societal and cultural stigma associated with sex, as well as limited knowledge among healthcare professionals about how to discuss or educate patients on sexual health, definitely are obstacles.”

The data add to the literature by confirming earlier studies showing similar gaps, she noted. They also serve as a reminder that more than a decade ago, the AHA released a scientific statement devoted to sexual activity and CVD, which can guide clinicians on how to approach the topic.

“Let’s hit the pause button and go back to incorporate a discussion of sexual health into the treatment plan,” Mieres stressed.

15. Pregnancy, aortic events, and neonatal and maternal outcomes

Background and Aims

This study aimed to evaluate the association between pregnancy and aortic complications and determine related maternal and neonatal outcomes.

Methods

Records of pregnancies and neonatal deliveries from the Taiwan National Health Insurance Research Database from 2000 to 2020 were retrieved. The incidence rate ratio (IRR) was calculated to evaluate the risk factors for aortic events. Survival analysis was conducted to compare maternal and neonatal mortality with and without aortic events.

Results

A total of 4 785 266 pregnancies were identified among 2 833 271 childbearing women, and 2 852 449 delivered neonates. In the vulnerable

and control periods, 57 and 20 aortic events occurred, resulting in incidence rates of 1.19 and 0.42 aortic events per 100 000 pregnancies, respectively. Pregnancy was established as a risk factor for aortic events (IRR: 2.86, $P < .001$). The 1-year maternal mortality rate was significantly higher in pregnancies with aortic events than in those without such events (19.3% vs. 0.05%, $P < .001$). Neonates whose mothers experienced aortic events had a higher late mortality (6.3% vs. 0.6%, $P < .001$).

Conclusions

The association between pregnancy and aortic events was established in this study. The results revealed that women are at risk of aortic events from the gestational period to 1-year postpartum. Maternal mortality was significantly higher in pregnancies with aortic events than in those without. A higher late mortality and more complications were noted for neonatal deliveries with maternal aortic events. Early awareness of pregnant women at risk of aortic events—especially those with concomitant hypertensive disorders of pregnancy, contributive family histories, or aortopathy—is crucial.

Key Question

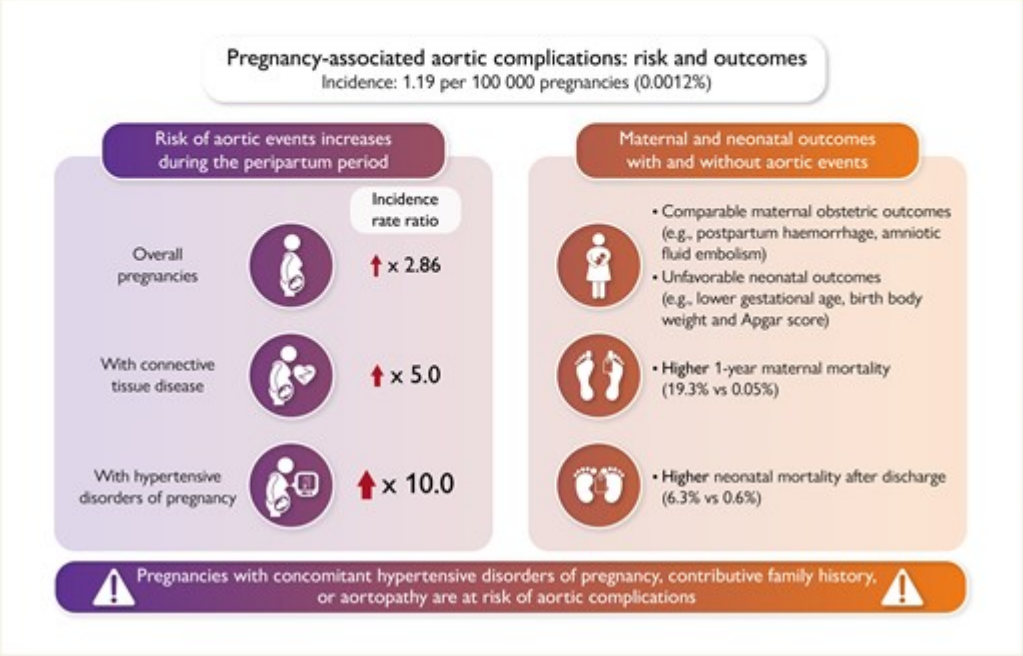
The association between pregnancy and life-threatening aortic complications (including dissection and aneurysm rupture) is still debated.

Key Finding

In this large observational study, pregnancy was associated with a higher risk of aortic events, especially in women with concomitant connective tissue diseases or hypertensive disorders of pregnancy. The 1-year maternal mortality rate was much higher in pregnancies with aortic events than in those without such events. Neonates whose mothers experienced aortic events had a higher late mortality.

Take Home Message

Women with pregnancy-associated hypertensive disorders or with connective tissue diseases should undergo an extended postpartum cardio-obstetric visit.



16. Sex, Race, and Rural–Urban Disparities in Ventricular Tachycardia Ablations

BACKGROUND

Ventricular ablation may be clinically indicated for patients with recurrent ventricular tachycardia (VT) and has been shown to decrease risk of recurrence and overall morbidity. However, the existence of disparities among patients receiving ventricular ablation has not been well characterized.

OBJECTIVES

In this study, the authors examined patients hospitalized with VT to determine whether disparities exist among those receiving ablations.

METHODS

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

RESULTS

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

CONCLUSIONS

The authors identified significant disparities in the delivery of ventricular ablations among patients hospitalized with VT. Overall, patients who were female or Black as well as those who were hospitalized at rural or nonteaching hospitals were significantly less likely to receive VT ablations during hospitalization.

17. The transformative power of women leaders in cardiology: breaking barriers and building excellence

Defining the problem

The lack of women in leadership within cardiology is a multifaceted issue and a symptom of the broader societal zeitgeist that is not unique to cardiovascular medicine. However, as a community of physicians striving to continue to enhance patient care, achieve equality, and drive innovation, this issue requires our curiosity and attention.

Despite equal numbers of women completing medical school, only 15% of cardiologists in Australasia are women, and only 5% of interventional cardiologists are women.1 Data across Europe are similar. Furthermore, women are less likely to be promoted into roles as head of departments, be involved in academia, or receive senior academic posts, even after confounders are adjusted for.2

This contribution advocates for women leaders within cardiology, examining the rationale for their role, barriers hindering their professional advancement, and considerations for the path forward.

The rationale for women in leadership

A lack of gender diversity in leadership has profound and negative impacts across multiple levels within cardiovascular medicine, from patient outcomes, to physician well-being, and workplace culture and productivity.

Firstly, equal representation of women in leadership in cardiology is critical to facilitate higher-quality care for patients. We know that gender plays a role in our interests, communication style, and ability to connect with patients, and research in healthcare demonstrates specific advantages when female physicians manage female patients, with greater reports of patient-centred care and improved patient satisfaction.3 However, the skewed and predominantly male workforce in clinical cardiology is a disadvantage for many female patients. For example, female patients treated by male physicians after myocardial infarction have worse outcomes than male patients, which is not the case when they are cared for by female clinicians.4 Indeed, the under-diagnosis and under-treatment of women with cardiovascular disease are well documented and systemic. The lack of women in academic research, coupled with a background of longstanding recruitment bias, is a contributing factor in the failure to design trials to address salient research gaps in women's health.5 Furthermore, within our communities, marginalized and intersectional groups often experience the worst health outcomes, highlighting the critical need to create leadership

teams that accurately reflect the culturally, linguistically, and gender-diverse communities we serve.

Gender inequality in medical leadership also impacts the professional advancement of female physicians, in a self-perpetuating cycle that perniciously undermines physician well-being. In a male-dominated industry where one-third of female cardiologists report sexual harassment in the workplace, the need to create a transformative culture shift becomes increasingly urgent.6 Combined with fewer mentorship opportunities and barriers to professional advancement, female physicians can be vulnerable to higher rates of burnout.7 Furthermore, women continue to experience the gender pay gap, a phenomenon that persists despite adjustment for variables such as age, qualification, and academic publications.2,5

At a macro-level, increased gender diversity in cardiology leadership will benefit our workplaces and communities, because diversity is a valuable human resource. Research shows that diverse workplaces demonstrate increased productivity, innovation, and profitability, and therefore, the mosaic of expertise that women can bring to complex cardiovascular problems can enhance innovation within the field.5 Furthermore, workplace culture is critical to performance, and gender diversity in cardiology leadership has been shown to facilitate a sense of belonging and improve staff well-being.1

What are the barriers?

Women in cardiology encounter a broad range of social, cultural, and structural barriers in their path towards leadership.

The imbalance of parental leave and caregiving responsibilities and inflexible training requirements emerge as structural barriers that reinforce gender roles. In Australasia, parental responsibilities are biased towards maternal caregiving, and while there is a move towards gender equality across Europe and Scandinavia, at a global level, women continue to provide a

disproportionate amount of the caregiving, further exacerbated by global disruptions such as the Covid-19 pandemic.8

Despite feminist advancements, medicine is still heavily influenced by traditional gendered models of leadership, and most female physicians report gender-based discrimination in their career.9 Often this discrimination is subtle, giving rise to the term 'micro-inequities' or 'micro-aggressions'. For example, female doctors are less likely to be introduced as 'Doctor' during grand rounds, are given less autonomy in the procedure room, and are less likely to receive referrals from male surgical colleagues due to cognitive biases.2 These interactions and patterns of behaviour culminate over time, shaping a healthcare culture that continues to devalue women as leaders.

The path forward

Fortunately, in recent years, a proliferation of academic literature coupled with more honest conversations has begun to cast light on this issue. Cardiology, which has traditionally been dominated by male voices, is experiencing a movement towards gender inclusivity, acknowledging and embracing the invaluable contributions that women leaders can bring to this field.

However, challenges remain, and to effectively enact change, a multifaceted approach is needed. Policy and cultural shifts as well as mentorship programmes emerge as levers for change.10 The establishment of robust mentorship programmes will be pivotal to providing a structured platform for knowledge exchange, skill development, and professional support for women. Simultaneously, the implementation of policies geared towards promoting gender equity is essential to dismantling systemic barriers. These policies should not merely be symbolic but transformative. Moreover, fostering a culture of inclusion is paramount, where diverse voices are not only heard but also actively valued and integrated into decision-making processes.

Healthcare leadership cannot remain a cultural microcosm. The way we communicate, build rapport, and view the world varies based on our individual stories and experiences, and a 'one size fits all' model fails to acknowledge the deep value in difference (*Figure 1*). It is time we reflect, dismantle barriers, and work towards a future of cardiology that champions leaders from all backgrounds.