

News in September 2023

1. From the Member Sections | Navigating Radiation Safety During Pregnancy: Practical Guidance For FITs

At the end of my first year of cardiology training, I (Melo) learned I was pregnant and faced a pivotal decision: continue with my current schedule or change my rotations to avoid radiation exposure. I had to quickly educate myself on best practices, current recommendations for fetal exposure and the experience of those with similar circumstances.










Although I had attended a lecture on radiation exposure and safety during my first year of training, I still felt I didn't know enough to make an informed decision. In fact, I had no sense of how much radiation exposure I already had because I hadn't worn a dosimeter. It turns out I'm not alone.

In a work-life survey conducted by the ACC, nearly one in three women cardiologists reported working in a department with no official policy for radiation safety in pregnancy; another one in three women were unaware of whether their department had any such policy.¹

The survey also revealed that radiation reduction and surveillance strategies are underutilized during pregnancy, with only 20% reporting wearing fetal badges and 24% using additional lead protection. There is a dire need to overcome the gap in knowledge about radiation safety and implementation of radiation safety practices among trainees.

Radiation exposure is a concern for all trainees, especially for those who are pregnant or are considering pregnancy. The decision to participate in rotations with a risk of radiation exposure during pregnancy can be daunting. Trainees must balance their desire to participate in cases and procedures with their desire to minimize risk to the fetus. This decision is very challenging and personal.

Figure. Level of Radiation Exposure From Different Sources

Exposure	Dose
Eating a banana 	0.1 uSv
Single tooth X-ray 	0.2 uSv
Dental Panoramic X-ray 	10 uSv
Flight from LA to NYC 	40 uSv
1 year living in brick building 	70 uSv
Probable fetal dose for entire gestation of working interventional woman 	90 uSv
Under-lead dose over entire gestation of working interventional woman 	300 uSv
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Legal dose limit for entire gestation 	5000 uSv
Known threshold for fetal injury 	100,000 uSv

uS, microSievert.
Adapted from womenasone.org and nea.gov.sg/our-services/radiation-safety.

Surprisingly, fetal dose exposure is very minimal, according to data from a radiation safety module developed by Women as One (Figure).² Furthermore, the risk of radiation exposure in the cath lab can be minimized by wearing appropriate protective gear and understanding basic radiation physics.

It's important to understand that a 0.25 mm lead apron absorbs approximately 96% of scatter radiation and a 0.5 mm lead apron absorbs about 98%. Wearing two lead aprons, also known as "double leading," can lead to musculoskeletal and back issues during pregnancy because of the added weight. To ensure tracking of potential radiation exposure to the fetus, trainees also should wear an additional dosimeter under their lead apron.

Of note, it's recommended that trainees discuss access to a dosimeter and any other concerns during pregnancy with their medical physicist and/or radiation safety officer. A dose report can be helpful in tracking monthly radiation exposure,³ and gauging the effectiveness of the lead apron.

Greater efforts should be made to increase radiation safety education and radiation exposure tracking during fellowship. Fellows can then feel empowered to make informed decisions regarding radiation exposure and practices to minimize exposure.

I chose to work in the cath lab during the second and third trimesters of my pregnancy because I had researched and reviewed the data and knew how best to mitigate potential risk. One of my proudest moments in training was answering a STEMI call at 36 weeks. While in the lab, I knew it would be a moment I would tell my daughter about one day because I felt so empowered!

2. Sex Differences in FFR- and IVUS-Guided PCI

Study Questions:

Sex differences in treatment and clinical outcomes according to physiology- or imaging-guided percutaneous coronary intervention (PCI) strategies remain unclear. Are there any sex differences in procedural characteristics and clinical outcomes in fractional flow reserve (FFR)- versus intracoronary ultrasound (IVUS)-guided PCI?

Methods:

The FLAVOUR (Fractional Flow Reserve and Intravascular Ultrasound for Clinical Outcomes in Patients With Intermediate Stenosis) trial was an investigator initiated, prospective, multinational, randomized controlled trial that compared FFR- and IVUS-guided PCI strategies. This is a secondary analysis of this randomized trial aimed to investigate the impact of sex on procedural characteristics, treatment, and clinical outcomes according to different strategies and treatment types (PCI vs. deferral of PCI, also referred to as deferral group). The criterion of FFR-guided revascularization was an FFR ≤ 0.80 . The criteria of IVUS-guided PCI were minimal lumen area (MLA) $\leq 3 \text{ mm}^2$; or $3 \text{ mm}^2 < \text{MLA} \leq 4 \text{ mm}^2$ and plaque burden $> 70\%$. The primary outcome was target vessel failure (TVF) at 24 months, defined as a composite of cardiac death, target vessel myocardial infarction, and target vessel revascularization. The Seattle Angina Questionnaire (SAQ) was used to quantify patient-reported outcomes regarding the symptoms and daily life.

Results:

Of 1,619 patients, 30% were women. Women showed a smaller MLA ($3.3 \pm 1.2 \text{ mm}^2$ vs. $3.5 \pm 1.3 \text{ mm}^2$, $p = 0.022$), a smaller plaque burden ($68.2 \pm 10.3\%$ vs. $70.9 \pm 10.0\%$, $p = 0.001$), and a less severe area stenosis ($69.0 \pm 8.6\%$ vs. $72.0 \pm 9.0\%$, $p < 0.001$). Compared with men, women had a smaller MLA, smaller plaque burden, and higher FFR. They had a lower PCI rate (40.8% vs. 47.9% , $p = 0.008$), which was mainly contributed by FFR guidance. Overall, women showed a lower TVF rate (2.4% vs. 4.5%). According to the treatment type, the cumulative incidence of TVF was lower in women than in men among those with the deferral of PCI (1.7% vs. 5.2%). Moreover, in multivariate regression analyses, sex was an independent predictor of TVF in overall patients (adjusted hazard ratio [HR], 1.96; 95% confidence interval [CI], 1.04-3.73; $p = 0.039$) and in the Deferral group (adjusted HR, 3.70; 95% CI, 1.44-9.50;

p = 0.007). However, this trend was not observed in patients who underwent PCI. In both women and men, there were no differences in clinical outcomes between the FFR- and IVUS-guided strategies.

Conclusions:

This study explored the impact of sex on physiology and outcomes in revascularization. The main findings were as follows: 1) Despite visually comparable % of diameter stenosis between sexes, an in-depth evaluation by FFR or IVUS showed less severe disease burden in women than that in men. 2) Women had a lower rate of PCI than men, which was attributed to the difference in patients guided by FFR. 3) Women experienced better clinical outcomes at 24 months than men, and such a favorable prognosis in women was mainly driven by the lower event rate in the Deferral group. 4) There were no differences in clinical outcomes between the FFR- and IVUS-guided strategies in both women and men.

Perspective:

The lack of sex-specific guidelines in the management of coronary artery disease (CAD) in women in terms of PCI and TVF has been challenging, especially since there is a unique phenotype of CAD in women, such as more nonobstructive plaques, higher resting flow, and less calcified lesions. In the current study, although visually estimated % of diameter stenosis was similar between the two sexes, an advanced evaluation by FFR or IVUS indicated that women had less severe disease burden than men. This study shows that despite similar diameter in both sexes, women had less severe MLA and IVUS was smaller in women, highlighting that angiogram might be overestimating the lesion. Incorporation of advanced imaging before PCI to assess lesion severity might provide better adjudication of treatment strategies (i.e., PCI vs. deferral), and lead to reducing the number of PCIs in intermediate stenosis. Sex-specific attention to lesion type and severity is needed for appropriate selection of patients.

3. Influence of Race/Ethnicity and Sex on Coronary Stent Outcomes in Diabetic Patients

Background

How diabetes mellitus (DM), race/ethnicity, and sex impact ischemic events following coronary artery stent procedures is unknown.

Methods

Using the PLATINUM Diversity and PROMUS Element Plus Post-Approval Pooled Study (N = 4184), we examined the impact of race/ethnicity, sex, and DM on coronary stent outcomes. Primary outcome was 1-year major adverse cardiac events (MACE) (MACE composite: death, myocardial infarction [MI], and target vessel revascularization).

Results

The study sample included 1437 diabetic patients (501 White men, 470 White women, 246 minority men, 220 minority women) and 2641 patients without medically treated DM (561 minority, 1090 women). Mean age (years) ranged from 61 in minority men to 65 in White women. Diabetic patients had a higher prevalence of atherosclerotic risk factors and comorbidities. Diabetic minority women (DMW; 70% Black, 27% Hispanic) had similar atherosclerotic risk factors to other diabetics, but experienced higher 1-year MACE (14.4% vs 7.5%, $P < .01$) and MI (4.3% vs 1.6%, $P < .01$) rates compared with patients without medically treated DM. No other diabetic cohort (White men, White women, minority men) showed an increased risk of MACE vs patients without medically treated DM. The incremental risk of MACE in DMW was associated with insulin use and persisted after risk adjustment (adjusted odds ratio 1.6 vs patients without medically treated DM; 95% CI, 1.0-2.5). Independent predictors of 1-year MACE included insulin use, hyperlipidemia, renal disease, and prior MI.

Conclusions

DMW face the highest risk of ischemic events following coronary stenting, driven, in part, by insulin use. Aggressive secondary prevention and strict glycemic control are imperative in this cohort, and further research is warranted to elucidate the biologic mechanisms underpinning these observations.

4. Sex-Related Differences in Leadless Pacemaker Implantation

BACKGROUND

The impact of sex in clinical and procedural outcomes in leadless pacemakers (LPMs) patients has not been investigated yet.

OBJECTIVE

To investigate sex-related differences in patients undergoing LPMs implantation.

METHODS

Consecutive patients enrolled in the i-LEAPER registry were analyzed. Comparisons between sexes were performed within the overall cohort and using an adjusted analysis with 1:1 propensity-matching for age and comorbidities. The primary outcome was the comparison of major complication rates; sex-related differences regarding electrical performance and all-cause mortality during follow-up were deemed secondary outcomes.

RESULTS

In the overall population (n=1179 patients; median age 80 years), 64.3% were men. After propensity-matching, 738 patients with no significant baseline differences among groups were identified. During a median follow-up of 25 (interquartile range [IQR] 24-39) months, female sex was not associated with LPM-related major complications (hazard ratio [HR] 2.03, 95% confidence interval [CI] 0.70-5.84, p=0.190) and with all-cause mortality (HR 0.98, 95% CI 0.40-2.42, p=0.960). LPM electrical performance resulting comparable between groups, excepting for a higher pacing impedance in women at implant and during follow-up (24-month: 670 [550-800] vs 616 [530-770] ohms, p=0.014), however remaining within normal limits.

CONCLUSIONS

In a real-world setting, we found differences in sex-related referral patterns for LPM implantation with an under-representation of women, although major complication rate, and LPM performances were comparable between sexes. Female patients showed higher impedance values, not showing any impact on the overall device performance. Electrical parameters remained within normal limits in both groups during the entirety of follow-up.

5. The impact of sex, body mass index and chronic kidney disease on outcomes following percutaneous coronary intervention

Introduction

Obesity, defined as a body mass index (BMI) ≥ 30 kg/m², is a metabolic disorder that affects roughly 40% of American adults [1]. It predisposes to diabetes, hypertension and hypercholesterolemia, all major risk factors for cardiovascular disease (CVD). It has also been shown to be an independent risk factor for coronary artery disease (CAD) [2 , 3]. In the general population and in metabolically healthy individuals, obesity has been associated with increased cardiovascular morbidity and mortality [4 , 5]. Since weight reduction is associated with an improved risk factor profile for CAD, primary prevention guidelines recommend weight loss in overweight and obese individuals [6].

Despite the well-known adverse effects of obesity on cardiovascular diseases, several epidemiological studies and meta-analyses have shown a paradoxical association between obesity and improved cardiovascular outcomes (“obesity paradox”) [3 , 789101112131415]. This phenomenon was first described in patients undergoing percutaneous coronary intervention (PCI) [3] and was subsequently shown in multiple cardiac and non-cardiac conditions, including atrial fibrillation [11], sudden cardiac death [12], heart failure [13] and acute coronary syndromes, among other conditions [14]. The apparent protective effect of obesity conflicts with the well-known harmful effect of obesity and its close association risk factors that have a deleterious effect on cardiovascular disease, hence the paradox. However, other studies have shown that the better outcomes observed in these patients could be

explained by younger age, larger coronary vessels, more aggressive secondary prevention and better renal function [8].

Multiple studies have shown that chronic kidney disease (CKD) has an adverse impact on the survival of patients with CAD and has been associated with poor outcomes and increased bleeding risk after PCI [15]. However, data on clinical outcomes among women with CKD undergoing contemporary PCI are scarce because of restrictive inclusion and exclusion criteria in randomized controlled trials. We investigated the relationship between sex, BMI and kidney function on bleeding complications in patients undergoing PCI. We also studied whether kidney function modified the effect of BMI on major bleeding outcomes and major adverse cardiac and cerebrovascular events (MACCE).

Methods

Data collection

Data was collected by the Northwell Health System for quality control submission to the American College of Cardiology (ACC) National Cardiovascular Data Registry (NCDR®). All patients who underwent PCI between December 15, 2010 and March 30, 2018 at six tertiary care New York hospitals were identified. Information was collected on baseline, clinical, angiographic, and procedural characteristics, in-hospital outcomes, and length of stay as required by the NCDR® reporting system. A dedicated heart team consisting of treating general cardiologist, interventional cardiologist and nursing staff evaluated in-hospital access-related complications and bleeding rates following the procedure and before discharge as per routine protocol. Data were abstracted from patients' charts and entered into a dedicated spreadsheet for statistical analysis. As per Section 164.514(a) of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, all patient reports were de-identified from protected health information. The Institutional Review Board obtained a waiver of informed consent under the 2018 Common Rule (45 CFR 46.116).

Definitions

Bleeding outcomes were based on a modified Bleeding Academic Research Consortium Criteria (BARC) [16 , 17]. Conventionally, BARC type 0 is defined as no bleeding after PCI; BARC type 1 is defined as nonactionable bleeding which does not cause the patient to seek treatment by healthcare professional; and BARC type 2 is defined as an actionable bleeding that requires intervention by healthcare professional. The NCDR® database only reports data for the current PCI-related hospital stay and does not capture readmissions for complications. Therefore, for this analysis, BARC type 1 patients were grouped with BARC type 0 and within the BARC type 0/1 category there would be no net change in baseline hemoglobin post procedure. BARC type 2 was defined as a hemoglobin drop <3 g/dL from baseline after the procedure. BARC type 3a was defined as a post-procedure hemoglobin drop ≥ 3 to <5 g/dL or

if a patient received a blood transfusion with a hemoglobin drop <5 g/dL during the hospital stay. BARC type 3b is usually defined as any overt bleeding with a hemoglobin drop ≥ 5 g/dL; or cardiac tamponade; or bleeding requiring surgical intervention or vasoactive agents. However, the NCDR® database does not report data on bleeding requiring surgical intervention or vasoactive agents, therefore for this analysis, BARC type 3b was defined as a hemoglobin drop ≥ 5 g/dL with or without blood transfusion or cardiac tamponade. BARC type 3c is defined as intracranial hemorrhage or intraocular bleed compromising vision. Intraocular bleeding is not reported by the registry. For our analysis, BARC type 3c was defined as any post procedural hemorrhagic stroke regardless of hemoglobin drop. BARC type 4 (coronary bypass graft-related bleeding) was excluded, as the NCDR® database does not report information on post coronary bypass graft surgery complications. BARC type 5 (fatal bleeding) was omitted due to a lack of recorded data on bleeding being the cause of death and absence of autopsy records. Due to limitation in sample size within each BARC category, patients were classified as having BARC <3 or BARC ≥ 3 (major bleed). MACCE was the combined endpoint of in-hospital death, post-procedural myocardial infarction, post-procedure cerebrovascular events (ischemic and hemorrhagic), and major bleeding. Normal BMI was <25 kg/m², overweight BMI was 25 to 29.9 kg/m², and obese BMI was ≥ 30 kg/m². Kidney function was assessed by the estimated glomerular filtration rate (eGFR) and calculated based on the latest equations from the Chronic Kidney Disease Epidemiology Collaboration 2021 (CKD-EPI). CKD was defined as eGFR of <60 mL/min/1.73 m² [18].

Endpoints

The primary outcome was major bleeding complications (BARC ≥ 3) and the secondary outcome was MACCE. Additional endpoints included post-procedure cardiogenic shock, mortality, need for post-procedure dialysis, peri-procedural bleeding (including access site, retroperitoneal, gastrointestinal, genitourinary), and post-procedural blood transfusion.

Statistical analysis

Due to the clustering of patients within hospitals, hierarchical generalized linear mixed models were used when assessing factors associated with odds of BARC ≥ 3 or MACCE. Due to the high intraclass correlation of procedures within patients, only the first procedure within the study period was selected from each patient for analysis. Clinical characteristics, outcomes and the multivariable model analysis were performed at patient level, whereas procedural characteristics were done at lesion level. To assess interaction on the multiplicative scale, an interaction term between BMI as a 3-level variable (normal BMI, overweight, obese) crossed with CKD status (eGFR <60 vs. eGFR ≥ 60) was entered into each hierarchical logistic regression model, along with the main effects of each variable. These models also included covariate adjustment for the following: sex, prior cardiogenic shock, STEMI, age, and presence of mechanical cardiovascular support and/or intra-aortic balloon

pump. The factors to include in the models were selected a priori based on clinical expertise and prior literature.

Potential three-way interactions were also evaluated for both endpoints of primary interest (BARC \geq 3 or MACCE): between BMI, CKD, and sex; BMI, CKD, and age; BMI, CKD, and STEMI; and BMI, CKD, and prior shock for each outcome. In the presence of a significant three-way interaction, stratified analyses on the third factor were performed (e.g., sex) since stratification by a factor is equivalent to entering a product-term between the stratum-factor with the other parameters in the model. This method was used in order to aid in the interpretation of the effect of the three-way interaction,

Lastly, only descriptive statistics on the incidence of post-procedure cardiogenic shock, mortality, need for post-procedure dialysis, peri-procedural bleeding (including access site, retroperitoneal, gastrointestinal, genitourinary), and post-procedural blood transfusion were computed. All analyses were carried out using SAS version 9.4 (Cary, NC), and statistical significance was set at $p < 0.05$.

Results

Between December 15, 2010 and March 30, 2018, a total of 39,918 procedures were performed in 31,116 patients across six New York metropolitan area hospitals. Thirty patients were excluded because of missing values for eGFR or BMI. Of the 31,086 patients, BARC criteria were calculated for 29,507 patients and MACCE rates were calculated for 29,575 patients. Among those with a calculated BARC score, there were 28,363 patients (96.1%) with BARC $<$ 3 and 1144 patients (3.9%) with BARC \geq 3 (major bleed). For the multivariable analysis, 28,336 patients who had BARC $<$ 3 and 1142 patients who had BARC \geq 3 were included.

Baseline clinical characteristics are shown in Table 1 . There were 6740 patients (21.7%) with an eGFR $<$ 60 mL/min/1.73 m² and 24,346 patients with a eGFR \geq 60 mL/min/1.73 m² . On average, CKD patients were older, male, with more comorbidities such as hypertension, diabetes, peripheral arterial disease, chronic pulmonary disease, and prior cerebrovascular disease. Within both groups (CKD and non-CKD) patients, there were significant differences in clinical characteristics according to BMI. Obese patients, regardless of their kidney function, were on average 6 years younger than their normal BMI counterparts, mostly female, black and also had more of the classic comorbidities including prior coronary intervention, diabetes, hypertension and dyslipidemia. Normal BMI CKD patients were more often on dialysis and had significantly lower left ventricular ejection fraction.

Table 1

Baseline patient characteristics (n = 31,086).

	No CKD (eGFR ≥60 mL/min/1.73 m ²) (n = 24,346)				CKD (eGFR <60 mL/min/1.73 m ²) (n = 6740)			
	BMI < 25 (n = 5393)	BMI 25-29.9 (n = 9815)	BMI ≥ 30 (n = 9138)	p-Value	BMI < 25 (n = 1639)	BMI 25-29.9 (n = 2582)	BMI ≥ 30 (n = 2519)	p-Value
Age, years, mean, ± SD	67.9 ± 11.6	64.8 ± 11.0	62.1 ± 10.7	<0.0001	75.51 ± 10.4	73.13 ± 10.6	70.11 ± 10.5	<0.0001
Female sex (%)	1677 (31.1)	2118 (21.6)	2575 (28.2)	<0.0001	654 (39.90)	878 (34.0)	1123 (44.58)	<0.0001
White race (%)	3152 (58.5)	6196 (63.1)	6507 (71.2)	<0.0001	979 (59.7)	1553 (60.2)	1630 (64.7)	<0.0001
Black (%)	498 (9.2)	896 (9.1)	1083 (11.9)		253 (15.4)	376 (14.6)	507 (20.1)	
Other race (%)	62 (1.2)	133 (1.4)	90 (1.0)		21 (1.3)	39 (1.5)	27 (1.1)	
Asian (%)	1246 (23.1)	1761 (17.9)	790 (8.7)		285 (17.4)	387 (15.0)	191 (7.6)	
Unknown race (%)	435 (8.1)	829 (8.5)	668 (7.3)		101 (6.2)	227 (8.8)	164 (6.5)	
Dialysis (%)	0	0	0	-/-	272 (16.61)	321 (12.43)	283 (11.24)	<0.0001
Hypertension (%)	4250 (78.8)	8138 (82.9)	7954 (87.0)	<0.0001	1513 (92.3)	2423 (93.8)	2420 (96.1)	<0.0001
Diabetes (%)	1789 (33.2)	3663 (37.3)	4218 (46.2)	<0.0001	737 (45.0)	1409 (54.6)	1736 (68.9)	<0.0001
Dyslipidemia (%)	4128 (76.6)	7982 (81.3)	7544 (82.6)	<0.0001	1377 (84.0)	2228 (86.3)	2248 (89.2)	<0.0001
Smoker active (%)	1167 (21.7)	1839 (18.7)	1852 (20.3)	<0.0001	182 (11.1)	243 (9.4)	252 (10.0)	0.21
Peripheral vascular disease (%)	477 (8.9)	708 (7.2)	643 (7.0)	0.0001	293 (17.9)	396 (15.3)	414 (16.5)	0.09
Chronic lung disease (%)	461 (8.6)	558 (5.7)	674 (7.4)	<0.0001	177 (10.8)	244 (9.5)	317 (12.6)	0.002

	No CKD (eGFR \geq 60 mL/min/1.73 m ²) (n = 24,346)				CKD (eGFR <60 mL/min/1.73 m ²) (n = 6740)			
	BMI < 25 (n = 5393)	BMI 25-29.9 (n = 9815)	BMI \geq 30 (n = 9138)	p-Value	BMI < 25 (n = 1639)	BMI 25-29.9 (n = 2582)	BMI \geq 30 (n = 2519)	p-Value
History of cerebrovascular disease (%)	579 (10.7)	817 (8.3)	708 (7.8)	<0.0001	323 (19.7)	452 (17.5)	421 (16.7)	0.04
History of myocardial infarction (%)	1195 (22.2)	2209 (22.5)	2085 (22.8)	0.65	498 (30.4)	761 (29.5)	734 (29.1)	0.68
Previous coronary intervention (%)	1657 (30.7)	3431 (35.0)	3245 (35.5)	0.71	597 (36.4)	1082 (41.9)	1117 (44.4)	0.27
Previous coronary bypass surgery (%)	658 (12.2)	1286 (13.1)	1057 (11.6)	0.005	346 (21.1)	578 (22.4)	520 (20.7)	0.30
Family history of coronary disease (%)	441 (8.2)	939 (9.6)	995 (10.9)	<0.0001	78 (4.8)	156 (6.0)	156 (6.2)	0.01
Ejection fraction, %, mean \pm SD	52.2 \pm 12.2	52.9 \pm 11.4	53.3 \pm 11.2	<0.0001	48.2 \pm 15.0	49.7 \pm 14.3	51.4 \pm 13.4	<0.0001

Procedural characteristics are shown in Table 2 . Normal BMI patients more often underwent an urgent or emergent intervention regardless of renal function status, whereas overweight and obese patients were more likely to present with unstable angina and underwent more elective coronary interventions. Obese and overweight patient required a higher volume of

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Admission source								
Emergency department (%)	1906 (35.4)	3265 (33.3)	2991 (32.8)	<0.0001	599 (36.6)	891 (34.5)	825 (32.8)	<0.0001
Transfer (%)	1059 (19.7)	1569 (16.0)	1481 (16.2)	<0.0001	398 (24.3)	511 (19.8)	436 (17.3)	<0.0001
Patient presentation								
Heart failure 2 weeks prior to admission (%)	446 (8.3)	626 (6.4)	746 (8.2)	<0.0001	417 (25.4)	547 (21.2)	608 (24.2)	0.0030
Status								
Emergent (%)	697 (12.9)	1155 (11.8)	892 (9.8)	<0.0001	174 (10.6)	271 (10.5)	180 (7.2)	<0.0001
Urgent (%)	3389 (62.9)	5894 (60.1)	5737 (62.8)		1125 (68.7)	1625 (62.9)	1666 (66.1)	
Salvage (%)	8 (0.2)	15 (0.2)	8 (0.1)		7 (0.4)	12 (0.5)	8 (0.3)	
Elective (%)	1298 (24.1)	2749 (28.0)	2500 (27.4)		331 (20.2)	674 (26.1)	665 (26.4)	
Indication								
Non-ST elevation infarction (%)	990 (18.4)	1583 (16.1)	1574 (17.2)	<0.0001	360 (22.0)	477 (18.5)	450 (17.9)	<0.0001
ST-elevation infarction (%)	666 (12.4)	1111 (11.3)	848 (9.2)		167 (10.2)	274 (1.6)	162 (6.4)	

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Unstable angina (%)	2877 (53.4)	5342 (54.4)	5128 (56.1)		859 (52.4)	1368 (53.0)	1449 (57.6)	

Procedural characteristics

Fluoroscopy time, min, median (Q1-Q3)	14.6 (8, 18)	14.8 (8.2, 18.3)	14.7 (8.1, 18.1)	0.55	15.88 (1.2, 12.7)	15.68 (8.6, 19.3)	15.33 (12.5, 19.1)	0.55
Contrast volume (ml), mean ± SD	138.6 ± 63.2	144.1 ± 62.1	148.7 ± 63.9	<0.0001	115.5 ± 59.0	121.5 ± 60.6	123.0 ± 63.0	<0.0001
Intra-aortic balloon pump (%)	184 (3.4)	259 (2.6)	188 (2.1)	<0.0001	74 (4.5)	124 (4.8)	70 (2.8)	0.0004
Impella® (%)	50 (0.9)	60 (0.6)	46 (0.5)	0.01	29 (1.8)	37 (1.4)	30 (1.2)	0.31

Access site

Radial (%)	1865 (34.6)	3904 (39.8)	3979 (43.6)	<0.0001	345 (21.1)	684 (26.5)	773 (30.7)	<0.0001
Femoral (%)	3528 (34.6)	5905 (60.2)	5154 (56.4)		1293 (78.9)	1896 (73.5)	1746 (69.3)	

Procedural medications

molecular weight heparin (%)	273 (5.1)	463 (4.7)	501 (5.5)	0.10	74 (4.5)	123 (4.8)	114 (4.5)	0.92
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Unfractionated heparin (%)	3357 (62.3)	6195 (63.1)	5757 (63.0)	0.65	957 (58.4)	1528 (59.2)	1493 (59.3)	0.70
Aspirin (%)	5243 (97.3)	9542 (97.2)	8866 (97.0)	0.90	1567 (95.7)	2488 (96.4)	2435 (96.7)	0.58
Bivalirudin (%)	3241 (60.1)	5696 (58.0)	5166 (56.5)	0.002	1040 (63.5)	1613 (62.5)	1542 (60.5)	0.13
Gp IIb/IIIa inh (%)	42 (7.8)	847 (8.6)	773 (8.5)	0.29	91 (5.6)	130 (5.0)	132 (5.2)	0.71
Clopidogrel (%)	4499 (83.5)	8065 (82.2)	7502 (82.1)	0.003	1452 (88.6)	2264 (87.7)	2209 (87.7)	0.53
Prasugrel (%)	323 (6.0)	733 (7.5)	701 (7.7)	0.003	33 (2.0)	82 (3.2)	92 (3.7)	0.06
Ticagrelor (%)	495 (10.5)	967 (11.3)	889 (11.2)	0.15	85 (6.0)	161 (7.4)	160 (7.5)	0.16

contrast regardless of the kidney function ($p < 0.0001$). Overall, non-CKD patients with normal BMI underwent more complex interventions that required intra-aortic balloon or Impella support, and although there was a similar trend for CKD patients, it did not achieve statistical significance. Most patients had femoral access, however radial use increased with BMI in both CKD and non-CKD patients. There were some subtle differences among the groups regarding target vessel and lesion characteristics (Table 3). In-hospital outcomes are shown in Table 4 . Normal BMI patients had increased MACCE rates when compared to overweight or obese patients, regardless of CKD status. All the individual components of the combined endpoint, such as in-hospital stroke, mortality, new heart failure and myocardial infarction were higher in normal BMI patients.

Table 2

Procedural characteristics (n = 31,086).

Table 3

Angiographic characteristics (n = 38,717 lesions). ^a

	No CKD (eGFR ≥60 mL/min/1.73 m ²) (n = 24,346)				CKD (eGFR <60 mL/min/1.73 m ²) (n = 6740)			
	BMI < 25 (n = 7103)	BMI 25-29.9 (n = 12,895)	BMI ≥ 30 (n = 11,826)	p- Value	BMI < 25 (n = 2164)	BMI 25- 29.9 (n = 3424)	BMI ≥ 30 (n = 3243)	p- Value
Lesions attempted or intervened								
Left main artery (%)	145 (2.1)	228 (1.8)	186 (1.6)	0.06	86 (4.0)	116 (3.4)	108 (3.4)	0.38
Proximal LAD (%)	1293 (18.4)	2236 (17.5)	1912 (16.3)	0.0009	357 (16.7)	558 (16.5)	494 (15.3)	0.32
Mid-distal LAD (%)	1887 (26.8)	3374 (26.4)	3151 (26.9)	0.69	530 (24.8)	779 (22.9)	786 (24.4)	0.23
Ramus (%)	117 (1.7)	243 (1.9)	246 (2.1)	0.11	39 (1.8)	79 (2.3)	74 (2.3)	0.40
Right coronary artery (%)	1917 (27.2)	3274 (25.6)	3112 (26.5)	0.04	583 (27.3)	910 (26.9)	874 (27.1)	0.94
Posterior descending artery (%)	326 (4.6)	736 (5.8)	686 (5.9)	0.0007	110 (5.1)	208 (6.1)	170 (5.3)	0.19
Circumflex artery (%)	1613 (22.9)	3126 (24.5)	2799 (23.9)	0.05	513 (24.0)	849 (25.1)	801 (24.9)	0.65
Graft interventions								
Left internal mammary artery (%)	20 (8.9)	32 (8.0)	15 (4.7)	0.12	7 (6.3)	11 (5.5)	19 (10.7)	0.14

	No CKD (eGFR ≥60 mL/min/1.73 m ²) (n = 24,346)				CKD (eGFR <60 mL/min/1.73 m ²) (n = 6740)			
	BMI < 25 (n = 7103)	BMI 25-29.9 (n = 12,895)	BMI ≥ 30 (n = 11,826)	p- Value	BMI < 25 (n = 2164)	BMI 25- 29.9 (n = 3424)	BMI ≥ 30 (n = 3243)	p- Value
Other graft (%)	205 (91.1)	367 (92.0)	34.55 (95.3)		104 (93.7)	189 (94.5)	158 (89.3)	0.14

Lesions characteristics

Bifurcation lesion (%)	501 (7.1)	885 (6.9)	775 (6.6)	0.36	135 (6.3)	194 (5.7)	195 (6.0)	0.66
Chronic total occlusion (%)	163 (2.3)	284 (2.2)	300 (2.5)	0.21	51 (2.4)	46 (1.3)	61 (1.9)	0.02
Class C lesion (%)	4215 (59.6)	7596 (59.1)	6918 (58.7)	0.46	1354 (62.9)	2037 (59.7)	1915 (59.3)	0.02

Coronary flow pre-procedure

TIMI ≤1 (%)	1037 (14.6)	1936 (15.1)	1705 (14.5)	0.67	277 (12.8)	428 (12.5)	327 (10.1)	0.002
TIMI = 2 (%)	818 (11.5)	1439 (11.2)	1326 (11.2)		248 (11.5)	364 (10.7)	324 (10.0)	
TIMI = 3 (%)	5240 (73.9)	9489 (73.8)	8767 (74.3)		1633 (75.7)	2621 (76.8)	2585 (79.9)	

a For all lesion-level analyses, the nesting of lesions within a procedure for each patient was not considered.

Table 4

Post-procedural outcomes (n = 31,086).

	No CKD (eGFR \geq 60 mL/min/1.73 m ²) (n = 24,346)				CKD (eGFR <60 mL/min/1.73 m ²) (n = 6740)			
	BMI < 25 (n = 5393)	BMI 25-29.9 (n = 9815)	BMI \geq 30 (n = 9138)	p-Value	BMI < 25 (n = 1639)	BMI 25-29.9 (n = 2582)	BMI \geq 30 (n = 2519)	p-Value
BARC \leq 2 (%)	4880 (90.5)	8945 (91.1)	8469 (92.7)	<0.0001	1457 (88.9)	2307 (89.3)	2305 (91.5)	0.0001
BARC 3a (%)	180 (3.3)	220 (2.2)	159 (1.7)		128 (7.8)	178 (6.9)	126 (5.0)	
BARC 3b (%)	38 (0.7)	32 (0.3)	35 (0.4)		17 (1.0)	18 (0.7)	13 (0.5)	
BARC 3c (%)	2 (0.04)	2 (0.02)	0 (0)		2 (15.0)	2 (0.08)	3 (0.1)	
MACCE (%) (Death/MI/stroke/bleed \geq 3)	553 (10.8)	810 (8.8)	669 (7.7)	<0.0001	246 (15.3)	347 (13.8)	281 (11.5)	0.001
In hospital stroke (%)	14 (0.3)	8 (0.1)	17 (0.2)	0.003	10 (0.6)	13 (0.5)	12 (0.5)	0.01
In hospital mortality (%)	32 (0.6)	31 (0.3)	23 (0.3)	0.003	38 (2.3)	37 (1.4)	29 (1.2)	0.001
Myocardial infarction (%)	332 (6.2)	555 (5.7)	476 (5.2)	0.05	96 (6.7)	152 (5.9)	139 (5.5)	0.83

	No CKD (eGFR \geq 60 mL/min/1.73 m ²) (n = 24,346)				CKD (eGFR <60 mL/min/1.73 m ²) (n = 6740)			
	BMI < 25 (n = 5393)	BMI 25-29.9 (n = 9815)	BMI \geq 30 (n = 9138)	p-Value	BMI < 25 (n = 1639)	BMI 25-29.9 (n = 2582)	BMI \geq 30 (n = 2519)	p-Value
Received \geq 1 unit blood (%)	116 (2.2)	115 (1.2)	95 (1.0)	<0.0001	108 (6.6)	140 (5.4)	108 (4.3)	0.005
Heart failure (%)	99 (1.8)	121 (1.2)	128 (1.4)	0.01	75 (4.6)	75 (2.9)	74 (2.9)	0.005
Cardiac tamponade (%)	10 (0.2)	8 (0.1)	9 (0.1)	0.17	6 (0.4)	2 (0.1)	5 (0.2)	0.11
Post-procedure dialysis (%)	4 (0.1)	8 (0.1)	8 (0.1)	0.96	8 (0.5)	23 (0.9)	15 (0.7)	0.24
Access site bleed (%)	56 (1.0)	73 (0.7)	47 (0.5)	0.001	30 (1.8)	42 (1.6)	37 (1.5)	0.66
Retroperitoneal bleed (%)	6 (0.1)	7 (0.1)	7 (0.1)	-/-	3 (0.2)	4 (0.2)	1 (0.04)	-/-
Genitourinary bleed (%)	5 (0.01)	7 (0.1)	3 (0.03)	-/-	6 (0.4)	4 (0.2)	4 (0.2)	-/-
Gastrointestinal bleed (%)	17 (0.3)	18 (0.2)	10 (0.1)	-/-	20 (1.2)	14 (0.5)	8 (0.3)	-/-
Cardiogenic shock (%)	73 (1.4)	75 (0.8)	60 (0.7)	<0.0001	38 (2.3)	47 (1.8)	27 (1.1)	0.01

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Multivariable analysis for factors associated with odds of BARC \geq 3 included sex, pre-procedure cardiogenic shock, STEMI, age, and presence of intra-aortic balloon pump and/or Impella® support. The multilevel logistic regression models failed to provide evidence of a 2-way multiplicative interaction between BMI and CKD on major bleeding outcomes of all post-PCI patients ($p = 0.66$). Presence of a significant 3-way interaction between sex, BMI, and CKD was found ($p = 0.02$). After stratification by sex, a significant interaction was noted between BMI, CKD, and female sex ($p = 0.03$) but not BMI, CKD and male sex ($p = 0.43$). Fig. 1 demonstrates how the presence of chronic kidney disease modifies effect of BMI on major bleeding when stratified by sex. Fig. 2 a shows the odds of BARC \geq 3 for females according to CKD status and BMI group, after adjusting for the other covariates in the model. Obese females with kidney disease had the lowest incidence of bleeding when compared with overweight or normal weight females with kidney disease with a predicted probability of 28%. Normal BMI and overweight female patients had greater probability of major bleeding than obese female patients, (32% and 36%, respectively). Among females without kidney disease, normal BMI patients had the greatest odds of major bleeding compared with obese or overweight females with a predicted probability of 24%. Overweight and obese females had the lowest odds of bleeding, with a predicted probability of 17% and 15%, respectively. However, after adjustment, it was significant only in the obese versus normal BMI group. Overweight and obese females with CKD had significantly greater major bleeding odds than overweight and obese females without CKD. Therefore, among females with CKD, BMI did not appear to have a role on major bleeding complications. Among females, the odds of BARC \geq 3 were greater among those presenting with STEMI, increased age, IABP and/or Impella® support or prior cardiogenic shock after covariate adjustment ($p < 0.0001$, $p = 0.0003$, $p < 0.0001$, and $p = 0.018$, respectively). Among males, the odds of BARC \geq 3 were greater among those presenting with STEMI, pre-procedure cardiogenic shock, increased age, or IABP and/or Impella® support after covariate adjustment ($p < 0.0001$ for each of these variables in male-stratified model) (Fig. 2 b). The interaction between sex and CKD was not evident among male patients. Irrespective of BMI, male patients with CKD had higher odds of bleeding. After adjustment, normal BMI male patients had greater odds of bleeding than overweight or obese male patients, regardless of CKD status.

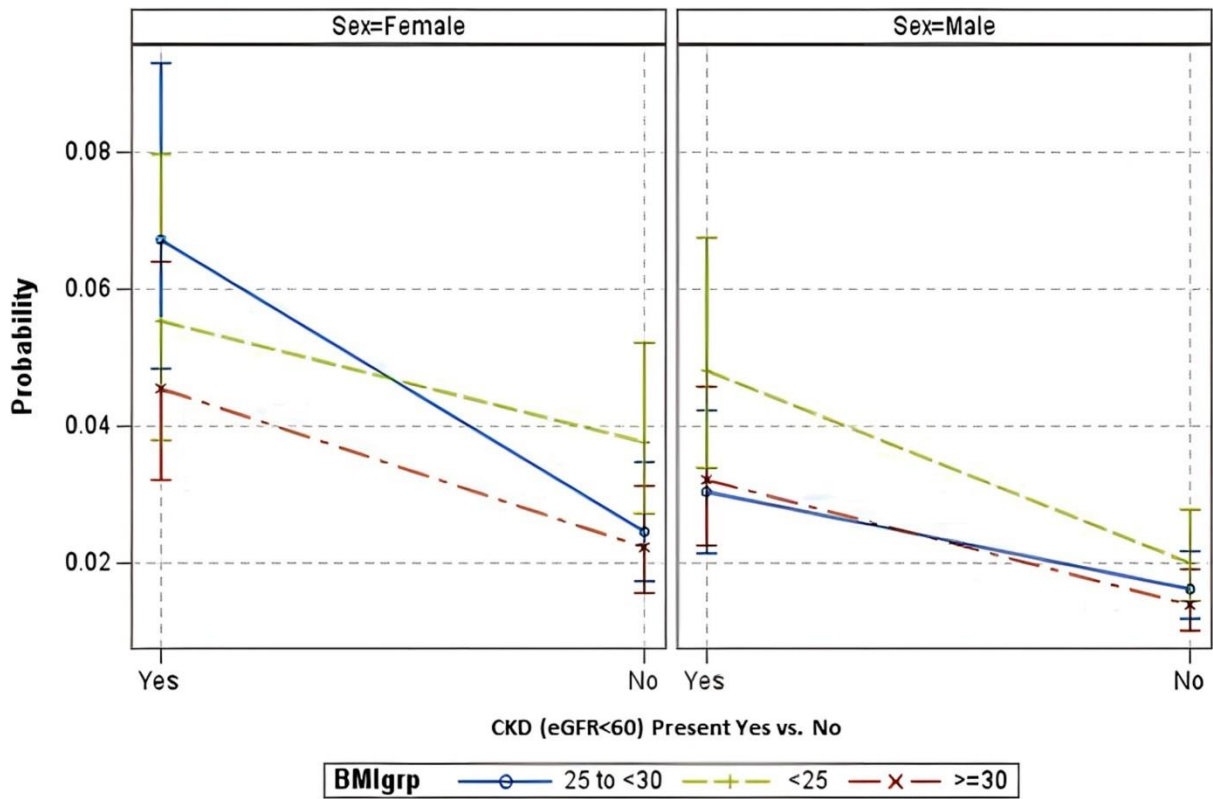


Fig. 1. Joint effect of body mass index, chronic kidney disease and sex on major bleeding outcomes.

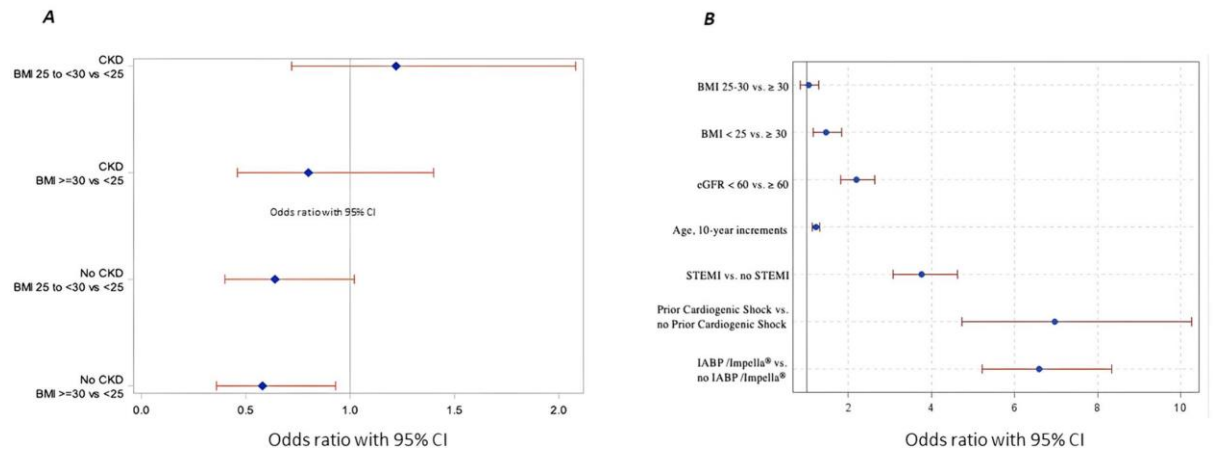


Fig. 2. Multivariable model for major bleeding outcomes stratified by sex: female 2A and male 2B.

Multivariable analysis for factors associated with odds of MACCE included sex, pre-procedural cardiogenic shock, STEMI, age and the presence of IABP and/or Impella® support (in addition to CKD and BMI status). Results failed to provide evidence of a multiplicative interaction between BMI and CKD on odds of MACCE ($p = 0.93$), nor any significant 3-way interactions. As a result, no interaction term was included in the final model for MACCE. The final model included the main effects for CKD status, BMI status, sex, pre-procedural cardiogenic shock, STEMI, age and the presence of IABP/Impella® support

($p < 0.0001$ for all). After adjusting for other factors in the model, the odds of MACCE were greater in normal weight patients vs. obese patients (OR: 1.27, 95% CI: 1.14-1.41), overweight patients vs obese patients (OR: 1.14, 95% CI: 1.03-1.25), CKD group vs. non-CKD group (OR: 1.39, 95% CI: 1.27-1.53), among females vs. males (OR: 1.35, 95% CI: 1.24-1.47), STEMI vs. other PCI indication (OR: 1.60, 95% CI: 1.41-1.82), pre-procedure cardiogenic shock vs. no pre-procedure procedure cardiogenic shock (OR: 4.48, 95% CI 3.30-6.09), and having IABP and/or Impella® vs. no mechanical ventricular support (OR: 5.17, 95% CI: 4.41-6.06) (Fig. 3). For each 10-unit increase in age, the odds of MACCE increased by 14% (OR: 1.14, 95% CI: 1.10–1.19), after covariate adjustment.

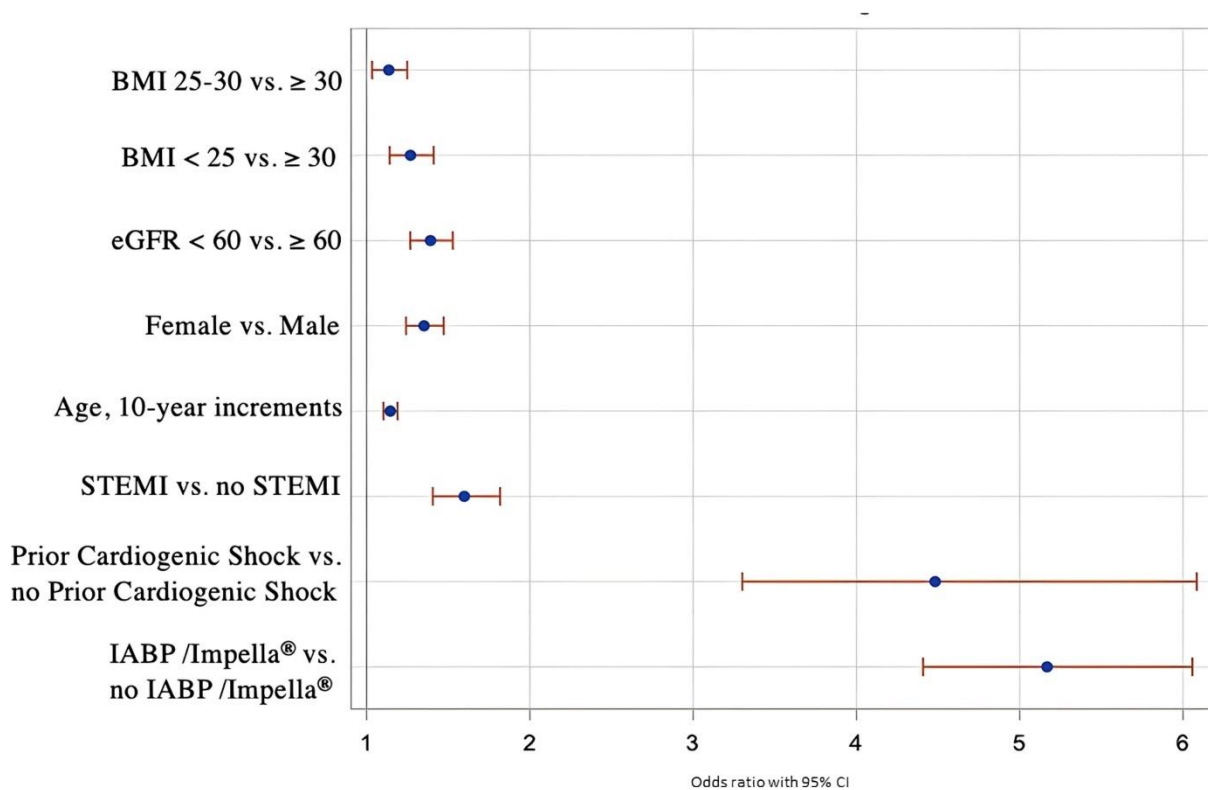


Fig. 3. Multivariable model for major adverse cardiac and cerebrovascular events (MACCE).

Discussion

The results of this large, contemporary analysis of patients undergoing PCI showed that: 1) major bleeding complications were rare (3.9% of subjects); 2) the joint effect of BMI, CKD, and sex influenced major post PCI bleeding outcomes; 3) after stratification by sex (female vs. male), the interaction between BMI and CKD status on the odds of major bleeding was observed in the female group only; 4) among female patients without CKD, normal BMI patients had the greatest odds of major bleeding compared with obese or overweight females; 5) overweight and obese females with CKD had significantly greater major bleeding odds than overweight and obese females without CKD, respectively; 6) among females with CKD, obese patients had the lowest odds of bleeding when compared with overweight or normal weight females, however it did not reach statistical significance after adjustment; 7) this interaction

was not evident among male patients and normal BMI male patients had greater odds of bleeding than overweight or obese patients, regardless of CKD status; and 8) irrespective of BMI, male patients with CKD had higher odds of bleeding than non CKD patients.

Both chronic kidney disease and obesity are major worldwide growing health issues affecting millions of patients. Both are considered significant risk factors for the development of cardiovascular disease, specifically coronary artery disease, which is the leading cause of morbidity and mortality in CKD patients. The combined interaction of BMI, CKD and sex and their impact on PCI bleeding outcomes in our study is interesting. There are few studies that address this issue and try to explain the impact of BMI between the sexes and most studies account for sex as a confounder and do not report stratified results [19]. It could also be argued that the obesity paradox is purely an epidemiological phenomenon driven by selection bias that has minimal effect for the practice of clinical cardiology [20]. The paradoxical association between obesity and certain cardiovascular outcomes could be attributed to potential confounders that were not collected as a part of the NCDR® registry such as increased lean mass, greater cardiorespiratory fitness, higher calorie reserve, larger coronary vessels, more secondary prevention measures, and more aggressive guideline directed medical therapies in these patients. In some studies, the “protective” effect of obesity was found in patients who were significantly younger than their normal BMI counterparts (almost 6 years younger) [3 , 4], had fewer comorbidities and therefore had less severe coronary artery disease, better left ventricular function, and thus better survival rates. Although we cannot ascertain causality, normal BMI patients may have had recent weight loss due to a severe illness (reverse causality). This illness may increase mortality, creating an apparent bias and appearance that overweight or obesity lower the odds of a bad outcome. Irrespective of the causation, the triple interaction in the present study is noteworthy and provides insight into developing management strategies among male and female patient populations with various BMIs and kidney functions undergoing PCI. In view of these results, every effort should be done to avoid bleeding complications, particularly in low BMI, female patients with CKD. The use of radial access, the choice of anticoagulation and optimal groin management in those patients that require femoral access PCI, may have a positive effect in terms of bleeding complications.

Bleeding, anemia, and the transfusion of blood products have all been associated with increased morbidity and mortality among patients undergoing PCI. In general, bleeding complications have not been included as part of the combined endpoint in interventional trials. However, previous studies in acute coronary syndrome patients undergoing an invasive strategy have shown that bleeding events are associated with worse outcomes and a 4-fold higher risk of one year mortality [19 , 21]. This has been formally recognized and current PCI guidelines require that all patients undergoing PCI should be evaluated for bleeding risk. This excess of bleeding events is more marked in female patients undergoing PCI. Data from

the CathPCI Registry® found that women had a nearly 2-fold increased risk of bleeding complications compared to their male counterparts (7.8% vs. 3.7%) despite adjusting for baseline clinical and procedural variables [21]. Although multiple randomized, controlled trials with antiplatelet medications have shown similar efficacy and safety outcomes between the sexes, results of real-world registries have consistently shown an increase in bleeding events among women, regardless of the type of P2Y12 antiplatelet agent used. Women undergoing PCI are usually smaller than men and lower BMI has been shown to be an independent predictor of PCI-related bleeding complications [22]. However, female sex has also been associated with increased platelet reactivity in response to agonists, with increased propensity to platelet aggregation and thrombosis implicating that female sex may be a risk factor for ischemic events [21]. Platelet reactivity studies have shown that higher BMI patients have higher on-treatment platelet reactivity and low BMI patients may have enhanced platelet suppression [23]. To complicate matters more, CKD has also been associated with high on-treatment platelet reactivity. Even moderate renal dysfunction has been independently associated with higher mortality and a trend towards stent thrombosis, suggesting that we should use more potent P2Y12 antiplatelet agents in women with CKD undergoing PCI [24 , 25]. These contradictory results, of higher bleeding complications and a simultaneously higher in vivo platelet reactivity among women with CKD and high BMI, remains unexplained.

The obesity paradox holds true for MACCE rates as well. Obese, non-CKD patients, and males had lower odds of MACCE following PCI. However, the joint effect of BMI, CKD, and sex did not seem to impact odds of MACCE. MACCE odds assessed individually were higher in normal weight patients vs. obese patients, overweight patients vs. obese patients, CKD vs. non-CKD and among females vs. male patients. STEMI, pre-procedure cardiogenic shock and the use of mechanical ventricular support were additional independent factors associated with increased odds of MACCE.

Our study provides an insight into the complex interaction which was noted only in the BMI, CKD, and female group on major bleeding outcomes. This complex interaction was not noted in the BMI, CKD, and male group on major bleeding outcomes. The combined impact of BMI, CKD, and sex (whether female or male) was not noted on MACCE outcomes.

Limitations

Although our findings rely on individual patient-level analysis, high-quality data abstracted for quality assurance purposes, the retrospective nature of the analysis is a major limitation. Individual patient data was methodically captured by dedicated personnel for quality assurance and not for research purposes. Patient level data analysis can overestimate post procedure complications. Kidney function was adjudicated based on the baseline eGFR at admission. There is always a concern that the calculation will be influenced by the acuity of

the disease and not be a true reflection of the steady kidney function. Under-reporting or over-reporting of post-PCI complications by either an overprotective or by an overzealous team are inherent limitations of medical records and therefore could have an impact on the data collected. Our database did not capture accurate recording of the guideline recommended medical therapy given to these patients and there was a lack of long-term follow up. Different therapies administered by different physicians and different compliance attitudes by patients can potentially affect clinical outcomes. Measures of frailty or comorbidities were not captured in the medical record and may represent unmeasured confounders that may contribute to the inferior outcome of normal BMI patients. BARC Type 4 and Type 5 bleeding complications were not collected, and underlying causes of death could underestimate the number of major bleeding events.

Conclusions

The present study shows that in patients undergoing PCI, there is evidence of a significant and complex 3-way interaction between BMI, CKD, and sex for major bleeding events but not for MACCE outcomes. After stratification by sex (female vs. male), the predicted probability of major bleeding for females is greater than for male patients, and for both sexes, greater among those with CKD, but BMI group influences these probabilities. Obese females with kidney disease had the lowest incidence of bleeding complications when compared with overweight or normal weight female patients undergoing PCI. This interaction was not seen in the male group. Therefore, CKD is a driver of major bleeding complications among female patients. Therefore, in these patients, every effort should be done to reduce bleeding complications, such as increasing the use of radial access, careful use of anticoagulation and optimal groin management in patients that undergo femoral access PCI. When analyzed individually, there were greater odds of MACCE rates in normal weight patients vs. obese patients, overweight patients vs. obese patients, and CKD patients vs. non-CKD patients. After co-variate adjustment, female sex, increased age, pre-procedure cardiogenic shock, STEMI, and the use of IABP/Impella ® were independent factors associated with greater odds of BARC ≥ 3 bleeding and MACCE rates.

6. Raising awareness about cardiovascular disease in women

Each year, cardiovascular disease maintains its status as the leading cause of morbidity and mortality in women.¹ In their most recent published statistics, the World Health Organization showed that ischaemic heart disease, stroke, and hypertension resulted in over 7.5 million deaths in women globally in 2019. This trend is similar to the mortality burden in men and is echoed by countries worldwide. Despite this, there remains a significant male predominance in practically all clinical trials measuring the safety and efficacy of investigations and management of cardiovascular disease, which ultimately directs clinical guidelines.

Coronary artery disease represents over 50% of the cardiovascular deaths of women, and over a third of all women in their fourth decade will go on to develop some degree of coronary artery disease. Women presenting with acute coronary syndromes (ACS), both ST and non-ST elevation myocardial infarction, suffer greater in-hospital mortality than men.²⁻³ Women are more likely to experience longer delays when it comes to presentation, investigation, diagnosis, treatment, and follow-up of coronary artery disease syndromes. Furthermore, women are less likely to receive the same guideline-directed therapy as their male counterparts who present with the same condition.

The problem

Why is there such a discrepancy between men and women in cardiovascular disease? Does this not represent a fundamental gender inequality and therefore implications for the human rights of women everywhere? The problem is, with to whom does the buck stop? Is it the public, clinicians, and policy-makers? Either way, we are all failing women everywhere. Two-thirds of all clinical research has been carried out in men. A review in 2018 of a broad spectrum of clinical trials for cardiovascular disease including heart failure, coronary artery disease, and ACS showed that women were under-represented in almost all.⁴ Furthermore, when they are included, women are more likely to be lost to follow-up during the trial period.

However, this problem goes far beyond the limitation of inclusion of women in clinical trials. A recent survey by the British Heart Foundation showed that there exist very real public misconceptions that cardiovascular disease, in particular stroke and ischaemic heart disease, is a problem mostly affecting men. The most universal symptom of ACS is chest pain, equally prevalent in women and men. It is curious then why studies have shown that women with symptoms of acute myocardial ischaemia typically present for medical assessment later than men. Could this phenomenon be explained by these public misconceptions? It is well established that delays in treatment of ACS increase mortality. A public mindset that our fathers and sons are exclusively ailed by 'heart attacks' is putting the lives of our mothers and daughters at critical risk.

Cardiovascular disease is associated with a multitude of risk factors, including smoking, hypertension, hypercholesterolaemia, and obesity. These remain important targets for intervention by public health and primary care physicians. These risk factors influence women differently to men. Women metabolize cholesterol differently to men, which contributes to a greater rate of development and progression of atherosclerotic cardiovascular disease. Women are less likely to uptake or maintain statin therapy. Smoking contributes an extra 25% risk of cardiovascular disease in women. Consumption of less fruit, vegetables, dairy, and fresh meat is associated with poorer cardiovascular outcomes in women. Furthermore, women are burdened by additional risk factors to men. Hormonal influences,

menopause, age of menarche, pregnancy, and pregnancy-related diseases such as gestational hypertension and diabetes⁵ all play a role in the additional cardiovascular risk to a woman. Hormonal influence and cardiovascular risk are even more important to those who are transgender.⁶

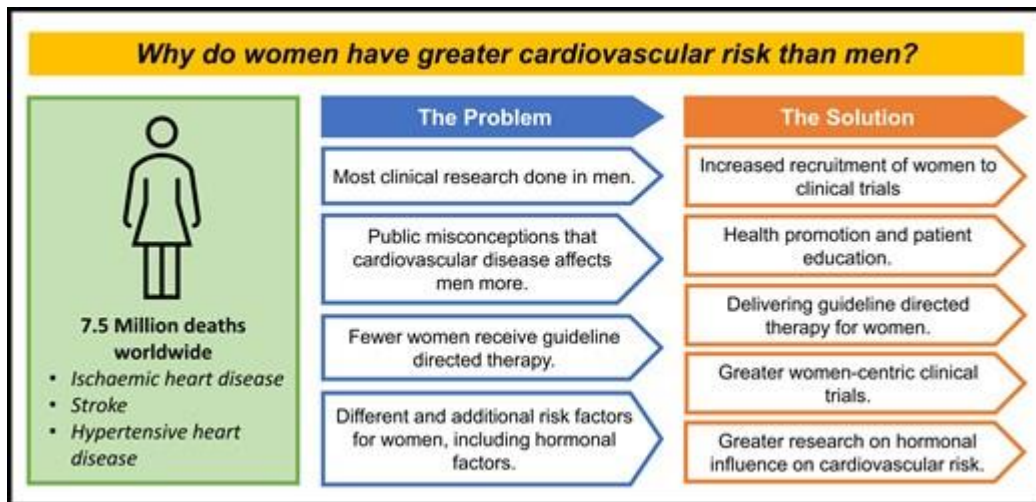
Women who suffer ACS are less likely to undergo percutaneous coronary intervention within the guideline-directed therapeutic window. This may be contributed to by the increased prevalence of non-obstructive coronary arteries in women, termed myocardial infarction with non obstructive coronary arteries or ischaemia with non obstructive coronary arteries.^{2,7} Alternative pathophysiology of the presenting ACS may blur the lines for clinicians to proceed with guideline-directed therapy; however, regardless of the underlying cause, women are less likely to be prescribed dual anti-platelet therapy, statins, and other secondary-prevention medications post-myocardial infarction than men. Fewer women are offered cardiac rehabilitation (CR) programmes following an acute coronary event. Women are also less likely to attend a CR session, particularly if they are from a black and minority ethnic background. Unfortunately, for those women who do attend a CR programme, the evidence suggests they do not gain the same level of benefit as men.⁸

The solution

In 2023, it is hard to believe that women still face significant gender inequality and inequity. Greater emphasis is needed to eradicate the stigma that cardiovascular disease is a man's domain. This may be achieved through greater promotion of health awareness by policy-makers, cardiovascular health charities, physicians, educators, and media; the list is endless. Outreach needs to focus on positive reinforcement that cardiovascular disease affects all and is actually worse for women and must aim to reduce the degree of 'fake news', which may ill-advise the public. Clinicians may facilitate this by encouraging women to attend their health checks (<50% of all patients currently attend these), encouraging health ownership by women in a similar vein that they may attend breast cancer and cervical screening appointments; and ensuring lifestyle modification and primary prevention is provided to those who are at greatest risk of cardiovascular disease.

Investigators who organize clinical trials must ensure greater gender equality in their recruitment. Reviewers of trial protocols should aim to highlight discrepancies in gender recruitment. More women-centric trials should be considered to focus on the investigation and management of cardiovascular disease in a vulnerable group who have greater and extra risk than men (see Figure 1).

Figure 1



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Central illustration

Studies have focussed on in-hospital ACS care variability, which has sought to find a solution to the overall greater morbidity and mortality suffered by women. A 2018 cohort study of 1272 patients presenting with ST elevation myocardial infarction (STEMI) showed that sex disparities of in-hospital adverse events including death were reversed following the implementation of a simple, standardized four-step STEMI protocol facilitating direct access to the cath lab for all upon presentation.⁹ This study suggests that something as simple as an unbiased systematic approach to facilitate universal patient care is an effective strategy to reduce the gender inequalities faced by women with cardiovascular disease. Another study showed that in older adults with invasive treatment of non ST elevation acute coronary syndrome, provision of guideline-indicated care and long-term clinical outcomes were similar between males and females.¹⁰ Such strategies should be adopted in more hospitals throughout the world.

Conclusion

Women are subject to gender inequality and inequity when it comes to their cardiovascular health. There are numerous reasons why this may be the case; however, in 2023, this problem should not exist. We have explored some practical solutions to some of these common problems in order to raise awareness of the effects of cardiovascular disease in women and hope that these health discrepancies are resolved with urgency.

7. Alcohol-Related Deaths Higher in Women

OPLINE:

Alcohol-related mortality rates have risen recently among both men and women, but the rate of increase has been higher among females across different demographic categories, including race/ethnicity, age, cause of death, and region.

METHODOLOGY:

In the past, men tended to have more alcohol-related complications, but evidence suggests that the sex gap is narrowing — a trend attributed partly to an increase in alcohol use, high-risk drinking, and alcohol use disorders among women, but it remains unclear whether this convergence extends to alcohol-related death rates.

Women generally have a higher percentage of body fat and a lower percentage of body water compared with men, resulting in higher alcohol blood concentrations, potentially increasing vulnerability to complications.

The study used national mortality data from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) and diagnostic codes to identify alcohol-related deaths in the US between 1999 and 2020.

Researchers abstracted age-adjusted mortality rates (AAMRs) by age, sex, race/ethnicity, cause of death (alcohol poisoning, alcoholic liver disease, mental and behavioral disorders due to use of alcohol, or other), and census region.

TAKEAWAY:

Between 1999 and 2020, 605,948 Americans died from alcohol-related causes, resulting in an AAMR of 8.3 per 100,000 persons (95% CI, 8.3 – 8.3 per 100,000 persons).

Men were 2.88 times more likely to die from alcohol-related causes than women. This sex disparity persisted across age, race/ethnicity, census region, and cause of death.

Overall, alcohol-related mortality trends were stable from 1999–2007 but increased by 3.0% per year from 2007–2018 and by 14.1% per year from 2018–2020.

Among males, the trend was stable from 1999–2009, with annual increases of 3.0% from 2009–2018 and 12.5% from 2018–2020. Among females, the trend was slightly different: a 1.0% per year increase from 1999–2007, followed by a 4.3% increase per year from 2007–2018 and an even larger increase of 14.7% per year from 2018–2020.

Alcohol-related mortality increased among males and females across all age groups, but among those younger than 60 years, the rate of increase in the most recent trend was higher among males. Among adults aged 65 years or older, the annual rate of change was higher among females.

IN PRACTICE:

Changing patterns of alcohol consumption among women is important to the understanding of related mortality trends, said the authors, who noted that women now drink more alcohol and they do so more frequently than they did in the past, likely because of the normalization of alcohol use by females in society.

8. Catch-Up HPV Screenings Help Detect Cancer in Women Over 65

A catch-up screening test for human papillomavirus (HPV) may improve cancer prevention and detection in women older than 65 years, according to a new study.

The findings, published on July 6 in *PLOS Medicine*, included women between ages 65 and 69 years in Denmark who had no record of cervical cancer screening or an HPV test in the previous 5 years.

"It may be valuable to get women above the current screening age to get this one-time catch-up HPV test if they haven't had one before," said Mette Tranberg, PhD, a cancer epidemiologist and researcher at Randers Regional Hospital in Denmark and lead author of the study. "That is valuable knowledge for healthcare providers and policy makers."

Cervical cancer in the United States is most often diagnosed in women aged 35-44 years, according to the American Cancer Society, with the average age at diagnosis of 50 years. The cancer rarely occurs in women who have undergone regular screenings.

Though current guidelines recommend that clinicians stop screening women for cervical cancer at age 65 years if their previous screening results have been normal, Tranberg said that many women do not get screened as they get closer to age 65 years.

A study from researchers at the University of California, Davis, found several factors contribute to older women not receiving adequate screening. Some women may think that they no longer need Pap smears after going through menopause, or they might have received a hysterectomy and think that they no longer require screening. And although Pap tests have built-in HPV screenings, these tend to be less accurate in postmenopausal women.

But women older than 65 years account for about 20% of new cervical cancer cases.

According to the Centers for Disease Control and Prevention, until women reach age 80 years, they are as likely to get cervical cancer as are younger women. Jack Cuzick, PhD, professor of epidemiology at Queen Mary University of London, said that the new data should inform patient care and public health efforts.

"People often don't realize HPV can last even if people haven't been sexually active," Cuzick said. "Even if somebody is nearing 70, it's probably still worth getting an exit test."

The Intervention Group

Study participants were assigned to two groups, one of which was invited to participate in a free HPV screening, either with their general practitioner or by ordering a vaginal self-sampling kit. The control group received standard care, which in Denmark, includes having the opportunity to undergo routine cervical cytology.

9. Robust Evidence' That Exercise Cuts Parkinson Risk in Women

Physical activity has been tied to a significantly decreased risk of Parkinson's disease (PD) in women, results of a large, long-term prospective study show.

Investigators found that among almost 99,000 women participating in the ongoing E3N study, those who exercised the most frequently had up to a 25% lower risk for PD than their less-active counterparts.

The results highlight the importance of exercising early in mid-life to prevent PD later on, study investigator Alexis Elbaz, MD, PhD, research director, French Institute of Health and Medical Research (Inserm), Paris, France, told Medscape Medical News.

This is especially critical since there is no cure nor disease-modifying treatments. The medications that are available are aimed at symptom reduction.

"Finding ways to prevent or delay the onset of Parkinson's is really important, and physical activity seems to be one of the possible strategies to reduce the risk," Elbaz said.

The study was published online May 17 in *Neurology*.

Direct Protective Effect?

Results from previous research examining the relationship physical activity and PD has been inconsistent. One meta-analysis showed a statistically significant association among men but a nonsignificant link in women.

The investigators note that some of the findings from previous studies may have been affected by reverse causation. As nonmotor symptoms like constipation and subtle motor signs such as tremor and balance issues can present years before a PD diagnosis, patients may reduce their physical activity because of such symptoms.

To address eliminate this potential confounder, the researchers used "lag" analyses, where data on physical activity levels in the years close to a PD diagnosis are omitted.

The study relied on data from the E3N, an ongoing cohort study of 98,995 women, born between 1925 and 1950 and recruited in 1990, who were affiliated with a French national health insurance plan that primarily covers teachers. Participants completed a questionnaire on lifestyle and medical history at baseline and follow-up questionnaires every 2-3 years.

In six of the questionnaires, participants provided details about various recreational, sports and household activities — for example, walking, climbing stairs, gardening, and cleaning. The authors attributed metabolic equivalent of task (MET) values to each activity and multiplied METs by their frequency and duration to obtain a physical activity score.

Definite and probable PD cases were determined through self-reported physician diagnoses, anti-parkinsonian drug claims, and medical records, with diagnoses verified by an expert panel.

Researchers investigated the relationship between physical activity and PD onset in a nested-case control study that included 25,075 women (1196 PD cases and 23,879 controls) with a mean age of 71.9 years. They found physical activity was significantly lower in cases than in controls throughout follow-up.

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

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

Highlights

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

11. Higher risk of adverse cardiovascular outcomes in females with type 2 diabetes Mellitus: an Umbrella review of systematic reviews

Background

Previous studies have shown that females with type 2 diabetes mellitus (T2DM) may have excess mortality risk compared to their male counterparts. An important next step to address the high global burden of T2DM and cardiovascular disease (CVD) is an umbrella review to summarize data on sex differences in cardiovascular outcomes for patients with T2DM and assess the strength of the evidence observed.

Methods and results

Medline and Embase were searched from inception till 7 August 2022 for systematic reviews and meta-analyses studying the effects of sex on cardiovascular outcomes in T2DM patients. Results from reviews were synthesized with a narrative synthesis, with a tabular presentation of findings and forest plots for reviews that performed a meta-analysis. 27 review articles evaluating sex differences in cardiovascular outcomes were included. Females with T2DM had a higher risk of developing coronary heart disease (CHD; RRR: 1.52, 95%CI: 1.32–1.76, $P < 0.001$), acute coronary syndrome (ACS; RRR: 1.38, 95%CI: 1.25–1.52, $P < 0.001$), heart failure (RRR: 1.09, 95%CI: 1.05–1.13, $P < 0.001$) than males. Females had a higher risk of all-cause mortality (RRR: 1.13, 95%CI: 1.07–1.19, $P < 0.001$), cardiac mortality (RRR: 1.49, 95%CI: 1.11–2.00, $P = 0.009$) and CHD mortality (RRR: 1.44, 95%CI: 1.20–1.73, $P < 0.001$) as compared to males.

Conclusions

This umbrella review demonstrates that females with T2DM have a higher risk of cardiovascular outcomes than their male counterparts. Future research should address the basis of this heterogeneity and epidemiological factors for better quality of evidence, and identify actionable interventions that will narrow these sex disparities.

12. Women With LVO Acute Ischemic Stroke Less Likely to Be Routed to Stroke Centers

Women with large vessel occlusion (LVO) acute ischemic stroke (AIS) are less likely to be routed to comprehensive stroke centers (CSCs) compared with men, despite presenting with more significant stroke syndromes, according to a study published online July 18 in the Journal of the American Heart Association.

Muhammad Bilal Tariq, M.D., from UTHealth McGovern Medical School in Houston, and colleagues conducted a cross-sectional study involving patients with LVO AIS to examine whether distance to CSCs, stroke severity, and sex are associated with direct-to-CSC prehospital routing. The authors analyzed 503 consecutive patients with LVO AIS from a prospectively collected multihospital Houston registry from January 2019 to June 2020.

The researchers found that 82 percent of the 503 patients with LVO AIS were routed to CSCs. Compared with men, women with LVO AIS were older (73 versus 65 years) and presented with greater National Institutes of Health Stroke Scale scores (14 versus 12). Women were less likely to be routed to CSCs compared with men (adjusted relative risk, 0.91); distance to nearest CSC of ≤ 10 miles was associated with an increased risk for routing to a CSC (adjusted relative risk, 1.38).

"We don't know exactly why women were less likely than men to be routed to comprehensive stroke centers, but we do know that gender is an implicit bias," a coauthor said in a statement. "Getting to the granular level of what went into a hospital's routing decision will be very important for future studies."

13. Early Pregnancy BP Predicts Hypertensive Disorders of Pregnancy

Early pregnancy blood pressure (BP) patterns plus standard clinical risk factors can better predict hypertensive disorders of pregnancy, according to a study published online July 12 in the Journal of the American Heart Association.

Erica P. Gunderson, Ph.D., M.P.H., from Kaiser Permanente Northern California in Oakland, and colleagues examined whether early pregnancy BP patterns can predict hypertensive disorders of pregnancy. The retrospective cohort included 249,892 participants with systolic BP <140 mm Hg and diastolic BP <90 mm Hg or a single BP elevation \leq 20 weeks of gestation. All participants had prenatal care at <14 weeks of gestation and a still or live birth delivery at Kaiser Permanente Northern California hospitals during 2009 to 2019. The sample was split into development and validation datasets (70 and 30 percent, respectively). In the validation dataset, predictive performance of multinomial logistic regression models for early-onset (<34 weeks) preeclampsia, later-onset (\geq 34 weeks) preeclampsia, and gestational hypertension was evaluated.

The researchers found that for predicting early- and later-onset preeclampsia and gestational hypertension, models with six systolic BP trajectory groups (0 to 20 weeks of gestation) plus standard clinical risk factors performed substantially better than risk factors alone (C-statistics, 0.747, 0.730, and 0.768 versus 0.688, 0.695, and 0.692, respectively), with excellent calibration.

"This evidence demonstrates the inherent value of early pregnancy BP patterns to identify individuals who may experience improved outcomes through higher vigilance and, ultimately, more effective interventions," the authors write

14. Association Between Maternal Glucose Levels in Gestational Diabetes Screening and Subsequent Hypertension

BACKGROUND

We assessed the association between maternal glucose levels in pregnancy and subsequent hypertension.

METHODS

This population-level, retrospective cohort study examined women aged 12 to 54 years with singleton pregnancies completed at \geq 29 weeks of gestation from October 1, 2008 to December 1, 2018 followed until March 31, 2019 in Alberta, Canada. Women were stratified by results in the 50-gram glucose challenge test and by 75-gram oral glucose tolerance test subtypes (normal oral glucose tolerance test, elevated fasting plasma glucose only [elevated fasting], elevated postload glucose only, or elevation in both fasting and postload glucose [combined]). Time to development of hypertension was modeled using Cox proportional hazards models.

RESULTS

Of 313 361 women, 231 008 (79.1%) underwent a glucose challenge test only while 60 909 (20.9%) underwent either an oral glucose tolerance test only or both. Nine thousand five hundred eighty (3.1%) developed hypertension, and 2824 (0.9%) developed cardiovascular disease over a median follow-up of 5.7 years. Every 1-mmol/L increase in glucose in the glucose challenge test increased the risk of subsequent hypertension by 15% (adjusted hazard ratio and 95% CI, 1.15 [1.14-1.16]). Among those who underwent the oral glucose tolerance test, the combined group conferred the highest risk of subsequent hypertension, followed by elevated fasting, then elevated postload glucose only (reference: glucose challenge test ≤ 7.1 mmol/L, adjusted hazard ratio [95% CI]: elevated postload glucose only, 1.83 [1.68-2.00]; elevated fasting 2.02 [1.70-2.40]; combined, 2.65 [2.33-3.01]). No significant associations between maternal glucose levels and cardiovascular disease were observed.

CONCLUSIONS

Increasing maternal glucose levels in pregnancy were associated with increasing risk of subsequent hypertension. These findings may help identify higher-risk women who should be targeted for earlier postpartum cardiovascular risk reduction.

15. Impact of Sex on CV Adaptations to Exercise: Key Points

The following are key points to remember from a review about the impact of sex on cardiovascular (CV) adaptations to exercise:

1. Exercise is associated with CV adaptations, which differ by sex and are observed for both athletes and the general population. This review by Petek et al., examines the effect of sex on CV adaptations and outcomes, including the impact of sex hormones on exercise performance. This review also outlines critical areas in need of further research.
2. Knowledge gaps stem from underrepresentation of female participants in athletic-based research, despite significant increases in the number of female athletes. In particular, preparticipation screening of athletes is unequally distributed in competitive sports.
3. Exercise training is associated with CV remodeling. Female athletes have smaller absolute left ventricular (LV) and right ventricular (RV) cavity dimensions as well as smaller LV wall thickness, and LV mass compared to males. However, when indexing to body surface area, female athletes no longer have smaller LV and RV cavity sizes versus male athletes, but still have smaller average LV mass. Overall, it appears that female hearts do not necessarily remodel 'less' but rather differently in response to

exercise by incompletely understood mechanisms. Decreased peak exercise systolic blood pressure (BP) in female athletes may impart a diminished pressure load on the heart and induce less hypertrophy relative to chamber enlargement. Alternatively, higher testosterone levels in males may lead to more LV hypertrophy.

4. In general, females have shorter QRS intervals and lower QRS voltage on electrocardiography (ECG) compared to males. Although data on athletes that compares sexes are limited, it is likely that differences in chest size, breast tissue, and cardiac size are contributors to ECG patterns, which appear less remodeled in female athletes. Although female athletes exhibit fewer training-related ECG changes, they are three times more likely to have “abnormal” anterior T-wave inversions than males.
5. Female athletes have a lower risk of sudden cardiac death compared to males, which is a similar finding in the general population. Male athletes appear to be predisposed to the development of coronary artery calcium (CAC) that is not observed in female athletes. The lack of excess CAC in female master athletes may be due to estrogen-mediated protection from coronary artery disease over midlife exercise exposure. Male master athletes also have a higher prevalence of myocardial fibrosis on cardiac magnetic resonance imaging. Possible mechanisms for less fibrosis in females include lower exercise BP and lower testosterone, given testosterone potentiates myocardial inflammation.
6. While moderate physical activity is associated with a reduced incidence of atrial fibrillation (AF) in both sexes, high doses of vigorous physical activity have been associated with a three- to five-fold increase in AF in males, which is not seen in females. However, female athletes with a large lifetime exercise exposure may be underrepresented among available studies.
7. Male athletes typically outperform female athletes by 10-35% starting around puberty. Lower testosterone in female athletes is associated with several differences in the CV determinants of exercise performance. Relevant to endurance sport, peak oxygen uptake is lower in females even accounting for smaller body size and is related to females’ lower exercise stroke volume, blood volume, and hemoglobin. Females’ muscle fiber composition and metabolism confer higher fatigue resistance and better short-term recovery.
8. The impact of variation in estradiol and progesterone over the menstrual cycle or the different phases of oral contraceptive pills (OCPs) on exercise performance is incompletely understood. Existing studies suggest that exercise performance is not substantially impacted by the menstrual or OCP phase, and that use of OCPs overall has at most trivial detrimental impact.
9. The use of exogenous testosterone and other androgens has been most extensively studied in males, but this also appears to improve lean mass and exercise

performance in females. Higher endogenous androgens in female athletes also appear to be associated with better performance in several specific exercise disciplines.

10. Emerging data suggest that several years of gender-affirming hormonal therapy (GAHT) in transgender females results in declines in running speed and muscular strength, but both typically remain higher than in cisgender females. The effect of GAHT on performance among transgender males is not well-defined.

16. Impact of Age and Sex on Outcomes in Patients With HFrEF

BACKGROUND

Age and sex influence treatment and outcomes in patients with heart failure (HF).

OBJECTIVES

The authors examined the associations of age and sex with clinical characteristics, background therapies, outcomes, and response to vericiguat in this post hoc analysis of 5,050 VICTORIA (Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction) patients with HF and reduced ejection fraction; 1,568 (31%) were ≥ 75 years of age, of whom 445 (24%) were women.

METHODS

Clinical characteristics were compared across age (<65, 65 to <75, and ≥ 75 years) and sex. The treatment effect of vericiguat was estimated by age and sex on the primary composite outcome (time to first HF hospitalization or cardiovascular death) using Cox proportional hazards regression.

RESULTS

Compared with younger patients, those ≥ 75 years of age had more class III and IV symptoms, higher N-terminal pro-B-type natriuretic peptide levels, and worse kidney function but had the lowest use of triple therapy. No sex differences in triple therapy existed by age, but achieving target doses of triple therapy was less likely in older patients. Men ≥ 75 years of age were more than twice as likely to receive defibrillators and 65% more likely to undergo cardiac resynchronization than women. The primary composite outcome was nominally lower in women than men across all age groups. Vericiguat dosing did not differ between sexes in each age group, and its beneficial effect on the primary endpoint was not modified by age (continuous age, $P_{\text{interaction}} = 0.169$; categorical age, $P_{\text{interaction}} = 0.189$); and sex (3-way interaction; $P = 0.847$).

CONCLUSIONS

Although elderly women received less intense background HF therapy than men, their prognosis was nominally better. The benefit of vericiguat was independent of age and sex. (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction)

17. Worldwide, Care for Women With Acute HF Falls Short

Around the globe, women hospitalized with acute heart failure (HF) are less likely than men to receive guideline-recommended therapies, diagnostic testing, and interventions to treat their condition, according to an analysis of the REPORT-HF registry. Worse, women also are more likely to receive medications that could actually lead to or worsen heart failure.

And while 1-year mortality didn't differ overall, researchers found that women were at a disadvantage in countries that had the greatest income inequality. In countries where wealth was distributed more evenly among residents rather than concentrated in the hands of a few, women were actually more likely to survive than men.

Senior author Carolyn S.P. Lam, MBBS, PhD (Duke-NUS Medical School and National Heart Centre, Singapore), said the study extends prior reports by adding contemporary data on sex differences in HF and exploring the impact of income/wealth distribution.

"Unfortunately, the sex disparities in treatment that we observed are very reminiscent of that seen with other forms of CVD," she told TCTMD in an email.

Lam advised: "Clinicians first need to be aware of these sex differences (both biological factors and social determinants of health), acknowledge any inherent biases, then address the gaps by considering standardization of clinical approaches regardless of sex."

Anu Lala, MD (Icahn School of Medicine at Mount Sinai, New York, NY), commenting on the study for TCTMD, said, "In many ways, it was a recapitulation of what we did and do know."

Even so, the results add many insights, she noted. "This is a very large, multicenter, multinational registry, which is why the data are even more compelling." The fact that the trends were consistent on an international scale suggests the differences in care are real, said Lala.

Led by Jasper Tromp, MD, PhD, MPH (National University of Singapore and Duke-NUS Medical School, Singapore), the study was published online this week in JACC: Heart Failure.

REPORT-HF Sex Gaps

Tromp et al examined data from the REPORT-AF registry, a global observational cohort study that enrolled 18,553 participants (39% women) from 44 countries across six continents over a 3-year period ending in March 2017. All were hospitalized with a primary diagnosis of acute HF.

Female patients in the database, compared with male patients, were more likely to have heart failure with preserved ejection fraction (40% vs 20%; $P < 0.001$) and had more-severe signs/symptoms at the time of their admission (dyspnea, orthopnea, and pulmonary rales). They also tended to be older (mean age 71 vs 65 years) and were more likely to have comorbidities (eg, hypertension, atrial fibrillation/flutter, valvular heart disease, and diabetes), though they had a lower prevalence of CAD.

Diagnostic tools and treatment varied by sex. Compared with men, women were more likely to receive an echocardiogram but less apt to undergo coronary angiography and cardiac stress testing, and they had a lower rate of PCI.

Female patients who had heart failure with reduced ejection fraction were less likely to be discharged on a mineralocorticoid receptor antagonist, though other medication use did not differ. Women were more likely than men to receive treatments with the potential to cause or worsen HF, such as short-acting inhaled sympathomimetics, diltiazem, and antidepressants (18% vs 13%; $P < 0.0001$). And finally, among eligible patients, women were less likely to receive an implantable cardioverter-defibrillator and/or cardiac resynchronization therapy (3% vs 7%; $P < 0.001$).

Overall, the risk of 1-year mortality was similar for men and women after accounting for potential confounders.

Using data from the World Bank, the researchers also looked at income levels for each country. There were no differences in 1-year survival between male and female patients when analyzed by geographic region, or by their country's income level.

However, income inequality did carry weight. In countries that had a low level of inequality, as defined by the Gini coefficient, women saw better survival than men (HR 0.82; 95% CI 0.69-0.98). That difference wasn't apparent for patients in countries with middle (HR 1.10; 95% CI 0.98-1.23) or high (HR 1.06; 95% CI 0.93-1.19) disparities in income, with a P value for interaction of < 0.001 . In North America, female patients actually were at higher risk than men of dying by 1 year (HR 1.25; 95% CI 1.01-1.54).

“Since country income inequality tracks well with a country-level gender pay gap, we postulate that that income inequality impacts women more than men, leading to greater limitations on access to high-quality treatment among women,” Lam explained.

Sex-Neutral or Sex-Specific?

Overall, the findings “emphasize an ongoing unmet need to address sex differences in HF management,” Tromp and colleagues say, suggesting that “sex-neutral interventions” such as electronic decision support tools or polypills could prove helpful.

Lala suggested that a “one-size-fits-all mentality” might not suffice. “We may indeed be at the point where we have to [offer] individualized care more so than we're doing currently,” she said, adding that gender and sex are key factors to consider. “I think we have to remain humble to know that it can't just be as protocolized as we would sometimes like it to be.”

Heart failure is unique in that respect, Lala continued. “Sex and gender affect every aspect of heart failure, arguably even more than the other subspecialties in cardiovascular disease.”

To start, she explained, there are sex-specific risk factors—such as autoimmune disease, pregnancy, and breast cancer-related therapies—that disproportionately affect women. “Then the manifestations are different, as well, with the predominance of heart failure with preserved ejection fraction,” she noted. “We know that the ejection fractions are higher for women in general compared to men. The QRS duration is a little shorter than it is for men.”

And then, as in cardiology as a whole, there's less utilization of devices and other invasive therapies among women compared with men.

To TCTMD, Lam said that more details on socioeconomic status, education level, and cultural norms—which were not captured in the current study—would also help shed light on the disparities in care.

She suggested, too, that implementation studies should test both sex-specific and sex-neutral approaches to HF care, a proposal set out in an editorial by Nosheen Reza, MD (University of Pennsylvania, Philadelphia).

“To overcome these seemingly colossal barriers to sex and gender equity in HF care, a potential way forward may be to construct standardized care paradigms, agnostic to patient sex, that are scalable across a diversity of care settings and cultures,” Reza writes. On the other hand, “another potential strategy may be to institute care protocols that acknowledge the sex differences in treatment that have been repeatedly demonstrated and incorporate nudges or other mechanisms that aim to circumvent provider- and system-level sex biases.”

18. Hormonal Birth Control, NSAID Use Together Linked to VTE

Women taking certain types of hormonal contraceptives may be more likely to develop venous thromboembolism (VTE) if they're also taking a nonsteroidal anti-inflammatory drug (NSAID), observational data from Denmark suggest.

In that high-risk category are the combined estrogen/progestin patch, vaginal ring, and tablets with 50 µg ethinyl estradiol, the antiandrogen cyproterone, or the progestins desogestrel, gestodene, or drospirenone. For women taking one of these drugs together with an NSAID, the likelihood of VTE was greater than those who combined an NSAID with either progestin-only formulations or no hormonal contraception.

“Use of birth control formulations containing estrogen (combined hormonal contraception) is an acknowledged risk factor for venous thromboembolism,” lead author Amani Meaidi, MD, PhD (Rigshospitalet, University of Copenhagen, Denmark), told TCTMD. Additionally, NSAIDs—a category that includes ibuprofen, diclofenac, and naproxen, and COX-2 inhibitors—are known to increase the risk of thrombosis by promoting platelet aggregation that can help activate the body's coagulation system.

As she and her colleagues note in their paper, published recently in the BMJ, the issue of how the two drug types might overlap to affect VTE risk is relevant given their wide use by women around the world.

“NSAID use is likely to be the most common co-medication to hormonal contraception use—still, no study has looked at the effect of concomitant use of hormonal contraception and NSAID on venous thromboembolic risk,” Meaidi wrote in an email.

“There are still important gaps in our knowledge on the cardiovascular risk of hormonal contraceptives,” she said. The extent of these gaps “is surprising considering the massive amount of daily users being exposed to these drugs. I think that the medical science [community] sometimes forgets that hormonal contraceptives first and foremost are pharmaceuticals—before being all the positive things that we [attribute] to them.”

I think that the medical science [community] sometimes forgets that hormonal contraceptives first and foremost are pharmaceuticals.Amani Meaidi

To dig deeper, the researchers turned to data from Denmark's national registries to track VTE events among 2 million women ages 15 to 49 between 1996 and 2017. They have medical

histories involving prior thrombotic events, cancer, thrombophilia, hysterectomy, bilateral oophorectomy, sterilization, or infertility treatment.

Hormonal contraceptives were divided by their expected risk based on prior studies. In addition to the aforementioned high-risk category, the researchers considered medium-risk products (all other combined oral contraceptives and medroxyprogesterone injection) and low/no risk methods (progestin-only tablets, implants, and hormone intrauterine devices).

Around a quarter of the women took NSAIDs, most often ibuprofen, while on hormonal birth control.

Over 21 million person-years, 8,710 of these women experienced a VTE, with 2.6% dying within 30 days of their event. Use of NSAIDs, when adjusted for confounders, was associated with higher VTE risk in women not on hormonal contraceptives, with an incidence rate ratio (IRR) of 7.2, as well as those on hormonal contraceptives considered to carry high, medium, and low/no risk, who had IRRs of 11.0, 7.9, and 4.5, respectively.

For every week of NSAID use, around four women out of 100,000 would develop VTE, the researchers estimated. Around two women out of 100,000 would do so for every week of high-risk hormonal contraceptive use, Meaidi explained. But for women who combined both drugs simultaneously, 23 out of 100,000 would have a VTE event with each week of use.

“This potentially suggests a synergistic drug interaction between these two drug classes,” she said.

For medium- and low/no-risk hormonal contraceptives on top of NSAIDs, there were an extra 11 and three VTEs, respectively, per 100,000 women per week of use.

Diclofenac in particular stood out as risky. When taken alone, around seven women per 100,000 weekly would develop VTE, as compared with three for ibuprofen and three for naproxen. When diclofenac was taken on top of a high-risk contraceptive, there were 28 added events per 100,000 women weekly, as compared with 25 for ibuprofen and 13 for naproxen.

Absolute Risk of 0.02% or Less

“Despite the high incidence rate ratios, the absolute risk of venous thromboembolic event in the first week after NSAID purchase remained low”—at 0.02%—“even in users of high risk hormonal contraception,” the investigators note.

Still, this issue is worthy of clinicians’ attention, said Meaidi, given how common the two medications are used and the severity of VTE.

To reduce the risk of developing VTE, she recommended that women—irrespective of whether they’re taking NSAIDs—switch from high-risk, combined-hormonal contraceptives to medium- or low/no-risk varieties. For pain relief, women can consider NSAID alternatives or nonpharmacological therapy, Meaidi added, and if NSAIDs are necessary, diclofenac should be avoided as it carries the highest CV risk.

Morten Schmidt, MD, PhD (Aarhus University Hospital, Denmark), in an editorial, agrees that the apparent synergism between NSAIDs and contraceptives has important ramifications for public health.

“Healthcare authorities and regulators should include these findings in their safety assessment of available over-the-counter diclofenac, and women using hormonal contraception and their clinicians should consider alternatives to NSAIDs for analgesia,” he suggests. “If treatment with NSAIDs is needed, agents other than diclofenac seem preferable, along with lower-risk hormonal contraceptives such as progestin-only tablets, implants, or intrauterine devices.”

Now researchers should replicate their study’s results in other populations and countries, said Meaidi. “Basic research should aim to investigate the potential mechanism of the interaction between the two drug classes.”

19. Hypertension, Anemia Contribute to Racial Disparities in Severe Maternal Morbidity

Hypertension and anemia contribute to racial disparities in severe maternal morbidity (SMM), according to two studies published online Sept. 7 in *Obstetrics & Gynecology*.

Stephanie A. Leonard, Ph.D., from Stanford University in California, and colleagues conducted a population-based study to examine the associations between chronic hypertension and several obstetric and neonatal outcomes. Data were included from 7,955,713 pregnancies, of which 2.1 percent were complicated by chronic hypertension. The researchers found that chronic hypertension was associated with adverse obstetric and neonatal outcomes, with the largest population attributable risks (PARs) seen for preeclampsia with severe features or eclampsia, acute renal failure, and pulmonary edema (22.4, 13.6, and 10.7, respectively). The adjusted PAR percentages for SMM were 5.0, 3.7, 9.0, 3.9, 11.6, 3.2, and 5.5 for American Indian-Alaska Native, Asian, Black, Latino, Native Hawaiian-Pacific Islander, White, and Multiracial-Other, respectively.

Iroque Igbinosa, M.D., from Stanford University in California, and colleagues examined the contribution of antepartum anemia to SMM using data from 3,863,594 births in California from 2011 through 2020. The researchers found that the incidence of antepartum anemia

was highest among Black patients followed by Pacific Islander patients (21.5 and 18.2, respectively); incidence was lowest for White pregnant patients (9.6 percent). The PAR percentage for antepartum anemia and SMM was highest for multiracial, Black, and Hispanic patients within each racial and ethnic group (21.4, 20.9, and 20.9 percent, respectively).

"The more evidence we use to standardize our approach to prenatal care, the more we can address and dismantle the effects of implicit bias on health care delivery," Igbinsosa said in a statement.

One author from the Leonard study disclosed payment as an expert witness; one author from the Igbinsosa study disclosed ties to industry.

20. Does Your Menopause Care Meet Your Patients' Needs?

In 2017, a survey of 20 U.S. residency programs in family medicine, internal medicine, and ob.gyn. showed that only 6.8% of residents felt they were being adequately prepared to manage menopausal patients effectively, including how to use hormone therapy (HT).

Of the 177 residents who responded to the survey, 102 (56%) were in either family medicine or internal medicine.

"My guess is that there has been no substantial evolution in medical training to this day," said lead survey study author Juliana Kling, MD, MPH, professor of medicine, chair of women's health internal medicine, and dean, Mayo Clinic Alix School of Medicine, Scottsdale, Ariz.

The survey showed that overall 98% of residents thought it was important to know about menopause. However, 34% said they wouldn't recommend HT in a severely symptomatic woman with no contraindications, and 60% said they wouldn't recommend HT until at least the natural age of menopause in a prematurely menopausal woman. Some even recommended against it.

"Hormone therapy is effective, and for most healthy women younger than 60, the benefits are going to outweigh the risks," said Dr. Kling. "We need to be comfortable, even in internal medicine, with prescribing hormones for the right women."

The researchers concluded that "residual ambivalence about [hormone therapy] on the part of educators" may have played a role in curriculums that didn't acknowledge the clinical relevance of menopause or include current evidence on the use of HT. Physicians should be taught to recognize menopausal symptoms, know the risks and benefits of HT and the alternatives, and how to select suitable candidates, they said.

Up to 80% of women in the United States are affected by menopausal vasomotor symptoms, but only one in four receive treatment, Dr. Kling pointed out. "Women will spend about a third of their lives after menopause, so being prepared to manage the consequences of

menopause, such as bone health, vaginal dryness and painful intercourse, and increased cardiovascular disease risk, is critically important to all of us caring for women," she emphasized. "These aren't just 'bothersome symptoms.'"

It is estimated that by 2060, there will be 90 million postmenopausal women in the United States. "Given the number of women who will experience symptoms of menopause and the considerable associated burden to their health and to the health care system, it is important to invest in educating future clinicians to provide evidence-based, comprehensive menopause management," said Dr. Kling and coauthors in a February 2023 review of menopause treatments.

HT is the standard for the treatment of hot flashes and night sweats, and is highly effective for the prevention of bone loss and managing genitourinary syndrome of menopause. Among the alternatives to HT, the nonhormonal pharmacologic fezolinetant (Veozah) was approved by the U.S. Food and Drug Administration last May.

21. Almost a Third of Female Surgeons Report Sexual Assault

Around two-thirds of female surgeons have experienced sexual harassment from colleagues, and almost one in three has been sexually assaulted by a colleague, according to a new report, described as "harrowing" and "horrifying" by NHS Providers and the British Medical Association.

Researchers from the University of Exeter and the University of Surrey set out to examine gender differences in surgical workforce members' experiences with sexual misconduct among colleagues in the surgical workforce over the past 5 years. They found that "women were significantly more likely to report witnessing, and [to] be a target of, sexual misconduct".

Most Women in Surgery Have Experienced Sexual Harassment

Almost two in three women (63.3%) reported being the target of sexual harassment and 29.9% said they had been sexually assaulted. Comparable figures for men were 23.7% and 6.9%. Well over four-fifths of participants — 89.5% of women and 81.0 % of men — had witnessed such events.

Harassment included jokes with sexual content; displaying sexualised pictures; unwanted/sexual e-comms, physical advances, or sexual talk; uninvited comments about the body; asking for a date despite previous refusal; being offered career opportunities for sex; being threatened for refusing sexual favours, and deliberately infringing body space.

Assault included forced physical contact for career opportunities – reported by 10.9% of women versus 0.7% of men; touching, excluding genitals/breasts; touching of genitals/breasts, and self-fondling by the perpetrator.

Being raped by a colleague was reported by 0.8% of women versus 0.1% of men (1.9% of women witnessing rape, versus 0.6% of men).

The survey, published in the British Journal of Surgery, concluded that sexual misconduct was "experienced widely, with women affected disproportionately". Women and men working in the NHS were "living different realities", the researchers commented.

Scale and Severity of Sexual Assault Against Female Surgeons "Atrocious"

In a statement, Dr Latifa Patel, equality lead at the British Medical Association, said it was "truly horrifying" to hear about women's experiences. "The scale and severity of sexual assault against female surgeons over the past five years, revealed by this survey, is atrocious. It is appalling that women in surgery are being subjected to sexual assault and sexual misconduct from their colleagues, at work and often whilst they are trying to care for patients."

The survey also showed that accountable organisations were not regarded as dealing adequately with sexual misconduct, with women's evaluations significantly lower than men's. Only 15.1% of women regarded the General Medical Council's response as adequate (versus 48.6% of men), with equivalent dismal figures for NHS Trusts (15.8% of women versus 44.9% of men), and the highest scores for the Royal Colleges still only 31.1% among women versus 60.2% among men.

In May this year, England's Health Secretary Steve Barclay urged NHS leaders to do more to protect health workers after a joint investigation by The BMJ and the Guardian revealed an "epidemic" of sexual misconduct in the NHS between 2017 and 2022.

The latest report was released just a week after the NHS launched a new 'sexual safety charter' promising to eradicate sexual harassment in the workplace. The charter would be "vital to helping protect staff", said Miriam Deakin, director of policy and strategy at NHS Providers. She described the findings as "harrowing" and pointed to "a clear and urgent need for action" to stamp out unacceptable behaviour at all levels. "There must be zero tolerance of sexual harassment of NHS colleagues," she said.

Report Makes "Incredibly Difficult Reading"

Asked to comment by Medscape News UK, Dr Binta Sultan, chair of NHS England's National Clinical Network of Sexual Assault and Abuse Services, said: "No one should experience

sexual abuse or assault in the workplace but unfortunately, we know inequality and sexual misconduct exists and is experienced disproportionately by our female colleagues across the NHS.

22. Does Your Menopause Care Meet Your Patients' Needs?

In 2017, a survey of 20 U.S. residency programs in family medicine, internal medicine, and ob.gyn. showed that only 6.8% of residents felt they were being adequately prepared to manage menopausal patients effectively, including how to use hormone therapy (HT).

Of the 177 residents who responded to the survey, 102 (56%) were in either family medicine or internal medicine.

"My guess is that there has been no substantial evolution in medical training to this day," said lead survey study author Juliana Kling, MD, MPH, professor of medicine, chair of women's health internal medicine, and dean, Mayo Clinic Alix School of Medicine, Scottsdale, Ariz.

The survey showed that overall 98% of residents thought it was important to know about menopause. However, 34% said they wouldn't recommend HT in a severely symptomatic woman with no contraindications, and 60% said they wouldn't recommend HT until at least the natural age of menopause in a prematurely menopausal woman. Some even recommended against it.

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Up to 80% of women in the United States are affected by menopausal vasomotor symptoms, but only one in four receive treatment, Dr. Kling pointed out. "Women will spend about a third of their lives after menopause, so being prepared to manage the consequences of menopause, such as bone health, vaginal dryness and painful intercourse, and increased cardiovascular disease risk, is critically important to all of us caring for women," she emphasized. "These aren't just 'bothersome symptoms.'"

It is estimated that by 2060, there will be 90 million postmenopausal women in the United States. "Given the number of women who will experience symptoms of menopause and the considerable associated burden to their health and to the health care system, it is important to invest in educating future clinicians to provide evidence-based, comprehensive menopause

management," said Dr. Kling and coauthors in a February 2023 review of menopause treatments.

HT is the standard for the treatment of hot flashes and night sweats, and is highly effective for the prevention of bone loss and managing genitourinary syndrome of menopause. Among the alternatives to HT, the nonhormonal pharmacologic fezolinetant (Veoza) was approved by the U.S. Food and Drug Administration last May.

Following the early negative reports from the Women's Health Initiative study of HT in 2002 and 2004, however, steep declines in HT prescription rates were seen among internists and family medicine practitioners. By 2009, only 18% of all HT prescriptions were written by primary care providers, and today, many remain wary about prescribing HT, despite evidence of its clinical value and safety.

23. Unexplored horizons on sex bias and progression of heart failure with preserved ejection fraction

'Heart failure with preserved ejection fraction (HFpEF) affects more women than men, suggesting sex to play a key role in disease evolution': this is an already established evidence in cardiovascular clinical practice.¹But, predicting changes in left ventricle ejection fraction (LVEF) towards values <50% that occur over time in HFpEF patients in both women and men remains one of the major unsolved clinical issues. But the million dollar question is: How it would be possible?

A recent study by Cao et colleagues² has provided an elegant mechanistic explanation supporting the hypothesis that the 'secret' of sex bias in HFpEF might be locked, at least in part, in heart mitochondrial function (Figure 1). The study has described a new experimental approach that integrates genetics and big data (RNA sequencing) technologies in both animal models and HF patients. The core hypothesis that mitochondria drive the sex bias in HFpEF-related diastolic dysfunction was investigated by using RNA-sequencing data of left ventricles from a previous study of isoproterenol-induced cardiomyopathy in a panel of genetically different inbred strains of female mice, known as Hybrid Mouse Diversity Panel (ISO-HMDP). Briefly, across the HMDP cohort the left ventricles of female mice showed lower levels of mtDNA content as well as lower levels of mitochondrial gene expression, as compared with male mice. An aspect of particular interest in this study was the validation of data from cardiomyocytes of mouse HMDP cohort in a previously published database of HF patients,³ even if irrespective from LVEF. From a clinical perspective, the most promising result arises from the acyl-CoA synthetase long chain family member 6 (Acsl6) gene encoding a mitochondrial protein involved in lipid metabolism. Data showed that Acsl6 expression levels were significantly lower in hearts of female than male mice. Besides, adenoviral-mediated administration of Acsl6 gene in the hearts of C57BL/6 J mice was sufficient to

decrease heart weight, E/e' ratio, and left ventricle mass supporting that *Acs16* overexpression may attenuate diastolic dysfunction in HFpEF.

24. CVD and Mortality in Black Women With V122I Transthyretin Gene Variant

Study Questions:

What is the relationship of transthyretin (TTR) V122I (pV142I) carrier status with cardiovascular disease (CVD) and mortality in a large cohort of postmenopausal women?

Methods:

The investigators analyzed 9,862 non-Hispanic Black/African American women, 9,529 noncarriers, and 333 TTR V122I carriers enrolled in the Women's Health Initiative at 40 centers in the United States. Women were generally healthy and postmenopausal at the time of enrollment (1993–1998). CVD was defined as a composite endpoint consisting of coronary heart disease, stroke, acute heart failure or CVD death, and all-cause mortality. CVD cases were based on self-reported annual mailed health updates. All information was centrally adjudicated by trained physicians. Hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained from adjusted Cox proportional hazards models.

Results:

Among 9,862 Black female participants (mean age, 62 years [IQR, 56-67 years]), the population frequency of the TTR V122I variant was 3.4% (333 variant carriers and 9,529 noncarriers). During a mean follow-up of 16.1 years (IQR, 9.7-22.2 years), incident CVD occurred in 2,229 noncarriers and 96 carriers, whereas 2,689 noncarriers and 108 carriers died. In adjusted models including demographic, lifestyle, and medical history covariates, TTR V122I carriers were at higher risk of the composite endpoint CVD (HR, 1.52; 95% CI, 1.22-1.88), acute heart failure (HR, 2.21; 95% CI, 1.53-3.18), coronary heart disease (HR, 1.80; 95% CI, 1.30-2.47), CVD death (HR, 1.70; 95% CI, 1.26-2.30), and all-cause mortality (HR, 1.28; 95% CI, 1.04-1.56). The authors found a significant interaction by age but not by blood pressure, heart rate, body mass index, or physical activity.

Conclusions:

The authors report that Black female TTR V122I (pV142I) carriers have a higher CVD and all-cause mortality risk compared to noncarriers.

Perspective:

This cohort study found that older Black women carrying the TTR V122I variant have a substantially elevated risk for CVD and mortality compared to noncarriers. Furthermore, the time to incident CVD and mortality was considerably shorter in carriers >65 years of age compared to noncarriers. Overall, these data suggest that Black women showing possible signs of amyloidosis should be screened for TTR V122I carrier status to ensure early therapy, as the availability of newer therapeutics may improve clinical outcomes. These findings are particularly important because they add to data on a substantially under-represented group of patients in amyloidosis studies, namely, Black women.

25. State-of-the-Art Review Examines Management of HF and Cardiomyopathy in Pregnancy

As maternal mortality continues to rise in the U.S., a comprehensive preconception risk assessment is crucial for women with heart failure (HF). HF and cardiomyopathy contribute to a high percentage of pregnancy deaths and multidisciplinary cardio-obstetric teams are necessary for improving maternal outcomes, according to a state-of-the-art review published Sept. 5 in JACC: Heart Failure.

Ersilia M. DeFilippis, MD, FACC, et al., discuss preconception counseling, risk stratification and management strategies for pregnant women with pre-existing or de novo HF extending to postpartum, the safety of HF medications during both pregnancy and lactation, and the management of women with left ventricular assist devices (LVADs) or after heart transplantation.

The authors note that “expert preconception counseling and appropriate risk stratification are necessary to provide individuals with the education and data needed for shared decision-making regarding the safety of pregnancy and potential outcomes,” and that using multidisciplinary cardio-obstetric teams to increase recognition and management of HF during pregnancy is vital in improving maternal outcomes.

They also write that “there are unique considerations for different subtypes of cardiomyopathy as well as women desiring pregnancy while LVAD support or after heart transplantation” and indicate further studies should “include how pregnancy can change the natural history of cardiomyopathy and how to improve maternal health systems in the peripartum and postpartum periods.”

26. USPSTF Recommends Screening for Hypertensive Disorders of Pregnancy

The U.S. Preventive Services Task Force (USPSTF) recommends screening for hypertensive disorders of pregnancy at each prenatal visit. This recommendation forms the basis of a final recommendation statement published in the Sept. 19 issue of the Journal of the American Medical Association.

Jillian T. Henderson, Ph.D., from the Kaiser Permanente Evidence-based Practice Center in Portland, Oregon, and colleagues conducted a systematic review to update the evidence on the effectiveness of screening for hypertensive disorders of pregnancy. The review included six fair-quality studies, with 10,165 participants, which compared changes in prenatal screening practices to usual care (routine screening at in-person office visits). The researchers found that the studies did not report significant differences in maternal and infant complications in association with alternate strategies versus usual care; for serious, rare health outcomes, estimates were imprecise. Home blood pressure measurement added to prenatal care visits was not associated with earlier diagnosis of hypertensive disorders of pregnancy. No difference in incidence was seen between the groups in three trials of reduced prenatal visit schedules.

Based on these findings, the USPSTF concludes that screening for hypertensive disorders in pregnancy with blood pressure measurements has substantial net benefit. Screening is recommended in asymptomatic pregnant persons throughout pregnancy (B recommendation).

"The task force continues to find that measuring blood pressure at each prenatal visit is an effective way to screen for hypertensive disorders of pregnancy," USPSTF member Esa Davis, M.D., M.P.H., said in a statement. "Because these conditions can cause serious health issues, screening is an important way to keep pregnant people and their babies healthy."

27. Women in cardiovascular imaging: a call for action to address ongoing challenges

Aims

The EACVI Scientific Initiatives Committee and the EACVI women's taskforce conducted a global survey to evaluate the barriers faced by women in cardiovascular imaging (WICVi).

Methods and results

In a prospective international survey, we assessed the barriers faced at work by WICVi. Three hundred fourteen participants from 53 countries responded. The majority were married (77%) and had children (68%), but most reported no flexibility in their work schedule during their pregnancy or after their maternity leave. More than half of the women reported experiencing unconscious bias (68%), verbal harassment (59%), conscious bias (51%), anxiety (70%), lack of motivation (60%), imposter syndrome (54%), and burnout (61%) at work. Furthermore, one

in five respondents had experienced sexual harassment, although this was rarely reported formally. The majority reported availability of mentorship (73%), which was mostly rated as 'good' or 'very good'. While more than two-thirds of respondents (69%) now reported being well trained and qualified to take on leadership roles in their departments, only one-third had been afforded that opportunity. Despite the issues highlighted by this survey, >80% of the participating WICVi would still choose cardiovascular imaging if they could restart their career.

Conclusion

The survey has highlighted important issues faced by WICVi. While progress has been made in areas such as mentorship and training, other issues including bullying, bias, and sexual harassment are still widely prevalent requiring urgent action by the global cardiovascular imaging community to collectively address and resolve these challenges.

28. Women Less Likely to Get CPR for Cardiac Arrest in Public Place Than Men

Women are significantly less likely to receive bystander cardiopulmonary resuscitation (BCPR) than men when experiencing out-of-hospital cardiac arrest (OHCA) in a public location, according to a study presented at the annual European Emergency Medicine Congress, held from Sept. 17 to 20 in Barcelona, Spain.

Sylvie Cossette, Ph.D., from the University of Montreal, and colleagues examined the interaction between age, gender, location, and rates of BCPR in OHCA patients. The analysis included 39,391 adult patients with nontraumatic, bystander-witnessed OHCA.

The researchers found that 54 percent of participants received BCPR, 23 percent of which occurred in public locations; 39 percent had an initial shockable rhythm, and 18 percent survived to discharge. There was a three-way interaction seen between patient gender, OHCA location, and age, which showed that in public locations, women were less likely to receive BCPR than men (adjusted odds ratio [aOR], 0.72; 95 percent confidence interval [CI], 0.64 to 0.81). There was no significant difference between men and women in private locations (aOR, 1.01; 95 percent CI, 0.96 to 1.06; P = 0.67). In public locations, there was no interaction between age and gender for OHCAs, but there was a significant interaction for OHCAs in private locations. Older age was strongly associated with reduced odds of receiving BCPR for men experiencing OHCA in private locations (aOR for a 10-year increase in age, 0.91; 95 percent CI, 0.90 to 0.93; P < 0.001). This association was weaker for women in private (aOR for a 10-year increase in age, 0.97; 95 percent CI, 0.94 to 0.99; P = 0.011).

"We don't know why this is the case," coauthor Alexis Cournoyer, M.D., also from the University of Montreal, said in a statement. "It could be that people are worried about hurting or touching women, or that they think a woman is less likely to be having a cardiac arrest."

29. New Risk Factors for Cardiovascular Disease in Women Emerging

Multiple emerging risk factors for cardiovascular disease in women must be recognized and assessed to provide timely diagnosis and treatment, according to Dipti N. Itchhaporia, MD, an interventional cardiologist in southern California. These risk factors include pregnancy complications, autoimmune diseases, depression, breast cancer, and breast arterial calcification.

During the session titled "Cardiac Care in Women: Emerging Risk Factors" at CardioAcademic 2023, the former president of the American College of Cardiology emphasized that gender equity in care for cardiovascular disease will only be achieved when risk factors are evaluated from a gender-dependent perspective and when assessments are broadened to include novel and unrecognized risk factors, not just traditional risk factors.

Itchhaporia also remarked that women and primary care clinicians must be educated on the symptoms of heart disease so that they can be on the alert and provide patients with comprehensive treatments when necessary.

"Cardiovascular disease remains the leading cause of death in women, at least in the United States, and globally the outlook is similar," she explained. "That's why we need to provide our patients with guidance and carefully investigate when they experience chest pain. We need to remember that smoking and obesity pose a higher risk for cardiovascular disease in women than in men. Taking these risk factors into account will really make a difference by allowing us to provide more timely and targeted care."

In her presentation, Itchhaporia noted that cardiovascular disease accounts for 35% of deaths in women worldwide. She reminded her audience that, according to The Lancet women and cardiovascular disease Commission, heart diseases in this population remain "understudied, underrecognized, underdiagnosed, and undertreated. Furthermore, women are underrepresented in cardiovascular [clinical practice]."

She mentioned this because, despite US legislation enacted between 1980 and 1990 that mandated the inclusion of women in clinical trials, women accounted for less than 39% of participants in cardiovascular clinical trials between 2010 and 2017. According to Itchhaporia, this situation limits the potential for developing tailored strategies and recommendations to treat the cardiovascular diseases affecting women..

Emerging Risk Factors

Itchhaporia pointed out that traditional risk factors have been known for many years. For example, 80% of women aged 75 years or younger have arterial hypertension. Only 29% receive adequate blood pressure control, those living with diabetes have a 45% greater risk of suffering ischemic heart disease, and obesity confers a 64% higher risk of developing ischemic heart disease in women vs 46% in men.

In addition to these factors, she noted that emerging factors must be assessed carefully. For example, women who experience pregnancy complications like gestational diabetes have a

higher risk for ischemic heart disease and type 2 diabetes. Women with hypertension and preeclampsia are at a threefold higher risk of developing ischemic heart disease.

"Pregnancy can really be a major stress test for the heart, and I believe that as healthcare professionals, we should all be asking women if they have had pregnancy-related complications. I don't think that's something we've been doing on a regular basis. Statistically, we know that 10%–20% of pregnant women report complications during pregnancy, and strong associations have been shown between gestational hypertension [and] preeclampsia."

30. Women interventional cardiologists: a glimpse into their extraordinary journeys

For me, the opening chords of the 1982 blockbuster Rocky III's 'Eye of the Tiger' theme song are one of the most instantly recognizable segments in the history of popular music even into 2023. Yet, this iconic award-winning film reaffirmed the stereotypical male hero, which lives on well into 2023. In this article, I would like to introduce women heroes who have also put on their boxing gloves to serve their communities during extraordinary times and through some unique challenges (Figure 2).

Dr. Shereen Al-Shaikh has worked as an interventional cardiologist in Bahrain since 2012. She graduated from the Arabian Gulf University in 2003 and completed her post-graduate training at The Heart Hospital-UCLH and The London Chest Hospital in the UK. She is the Head of the Coronary Care Unit at Mohammed Bin Khalifa Bin Salman Al Khalifa Specialist Cardiac Centre and a clinical lecturer at the Arabian Gulf University. Recently, at the GulfPCR-GIM meeting in Dubai 2022, she led the initiative of Gulf Women in Intervention (Gulf-WIN). Her clinical interests include interventions in adult congenital heart disease and cardiovascular diseases in women.

What challenges did you come across during your career?

The most difficult challenge I faced was during the pandemic when I was assigned as the head of a newly established COVID-19 center. This 40-bed unit, which included 15 ICU beds, was a tremendous undertaking, especially early in the pandemic when little guidance was available on management pathways for the COVID-19 infection. Adapting to this new role was a daunting task and, at times, challenging, especially given the responsibility I had to bear personally. We worked closely with the national task force and the Bahrain team to continually update the required treatment protocol. In addition, managing the team of residents, nurses, and allied health staff added to the complexity during these difficult times.

Several challenges I faced included dealing with this novel, deadly virus and the vast data that rolled in nearly every day. Understanding the data and discerning its validity; dealing

with my team's anxiety, fear of uncertainty, and heavy workload; and continuously monitoring my team's safety and performance and obtaining ways to motivate and maintain a good working spirit were particularly difficult. Finally, it was very difficult being entirely isolated from my family and close friends alongside the continuous work and stress of monitoring patients' status and reporting to the national operational room twice daily.

What are your aspirations?

Self-growth and personal improvement in my field as an interventional cardiologist is my priority. In addition to clinical work, I hope to grow as a teacher and a role model to my students at the university. Also, my role as a faculty speaker in international interventional meetings is a forum to showcase what female interventionalists can accomplish in our part of the world and to help empower women in the field of cardiology worldwide. I aim to educate and spread awareness regarding cardiovascular disease, especially in women, for better recognition and management. In addition, I plan to establish an adult congenital heart disease unit to provide the best care for this complex group of patients.

Dr. Nouf Alanazi is an interventional cardiologist who was appointed as the director of the cardiac center of the oldest university in the Kingdom of Saudi Arabia. She graduated from King Saud University and went on to complete her cardiology and interventional cardiology training in Canada. Despite the challenges that she faced in a male-dominated field, she rose up to the challenge of leading the center in the capital city of Riyadh, an experience which she describes as both extremely rich and enlightening.

What were the ingredients for your success as a leader and administrator?

I adopted the critical element of patient-centered leadership which was the core ingredient for her success. Fostering a healthy work environment and engaging the staff to work together toward a clear vision and a well-formulated set of strategies that revolve around these core values and ensuring it is cascaded smoothly and consistently across all institute levels were my primary goals during my first year as a director. Coupled with authenticity, confidence, perseverance, courage, and mentorship, I not only made my mark but also paved the way for my successors. This was a critical phase in my career as I was young with my instinct and prayers to guide me as a woman.

Dr. Rasha Al-Bawardy is an interventional, structural cardiologist and assistant professor at the National Guard Health Affairs, Jeddah, Saudi Arabia. She obtained her MD from The George Washington University in Washington D.C. and her post-graduate internal medicine residency at the Cleveland Clinic Foundation. She then completed her cardiology fellowship training at Montefiore Medical Center/Albert Einstein College of Medicine, where she served

as a chief fellow. She did 3 years of interventional cardiology fellowship and coronary, structural, and vascular interventions at the Massachusetts General Hospital/Harvard Medical School. Aside from her clinical work, she is currently a team member of the international early career work group under the American College of Cardiology as well as a board member of the Saudi Group for Cardiovascular Prevention and Rehabilitation under the Saudi Heart Association. She has interest in medical missions and recently provided cardiovascular support to pilgrims attending the annual Islamic Hajj.

Tell us about one of the most memorable times of your career as an interventional cardiologist?

Having the honor to serve as one of six interventional cardiologists during the Hajj (Pilgrimage) in 2022 has been by far one of the best experiences I have had in my career. Hajj is one of the five pillars of Islam and performed at a particular time of the year once in a person's lifetime. Muslims gather from all around the world in the holy city of Makkah (Mecca) to perform the Hajj rituals, which span 5 days. In order to ensure all the needs of the pilgrims (usually between 2 and 3 million), are met, the Saudi government spends significant amounts of time, effort, and money on healthcare along with other sectors. There is only one cardiac tertiary hospital in Makkah that has three cardiac catheterization laboratories. A successful cardiac team coverage has been established for years and focuses on providing a 24/7 catheterization service and has been shown to significantly reduce cardiac mortality.¹ During my shift, the cases kept coming with their unique challenges: multiple cardiogenic shock with acute coronary syndrome patients requiring percutaneous mechanical support devices, ventricular tachycardia that required mechanical support and percutaneous revascularization later, complex calcified lesions, many acute coronary syndrome who are unstable with multivessel and left main disease, severe symptomatic pulmonary valve stenosis requiring valvuloplasty, and severe symptomatic aortic stenosis requiring transcatheter aortic valve replacement. Decisions had to be made on the spot for some cases, but also two dedicated heart team meetings were scheduled every day at the beginning of every shift for those stable patients. The efficiency of the current system allowed the even distribution of more than 30 cases in some days. The teamwork spirit was astonishing from physicians, nurses, technicians, coordinators, paramedics, and other hospital workers who made the transition from case to case proficiently. I was privileged to be able to help patients from all over the world: Saudi Arabia, Qatar, Oman, Yemen, Morocco, Egypt, Ghana, Indonesia, Thailand, Turkey, India, Pakistan, the USA, France, and Iran in a span of 2 weeks.

What was the most challenging part of that experience?

Despite the complexity of the cases and dealing with very critically ill patients, the language barrier/literacy were an impediment with some patients. Although we had translators in the

hospital, there were some uncommon languages that no one knew and made the communication very challenging. The hospital provided them with the discharge medications for free along with medical reports and digital copies of their angiograms to be able to follow-up in their respective countries upon their return. In spite of all this, there is no comparable joy to seeing your sickest patients walk out of the hospital and continue their Hajj rituals.

31. Sex- and age-related differences in outcomes of patients with acute myocardial infarction: MINOCA vs. MIOCA

Aims

The aim of the study is to evaluate the impact of sex on acute myocardial infarction (AMI) patients' clinical presentation and outcomes, comparing those with non-obstructive and obstructive coronary arteries (MINOCA vs. MIOCA).

Methods and results

We enrolled 2455 patients with AMI undergoing coronary angiography from January 2017 to September 2021. Patients were divided according to the type of AMI and sex: male (n = 1593) and female (n = 607) in MIOCA and male (n = 87) and female (n = 168) in MINOCA. Each cohort was further stratified based on age (\leq / $>$ 70 years). The primary endpoint (MAE) was a composite of all-cause death, recurrent AMI, and hospitalization for heart failure (HF) at follow-up. Secondary outcomes included all-cause and cardiovascular death, recurrent AMI, HF re-hospitalization, and stroke. MINOCA patients were more likely to be females compared with MIOCA ones ($P < 0.001$). The median follow-up was 28 (15–41) months. The unadjusted incidence of MAE was significantly higher in females compared with males, both in MINOCA [45 (26.8%) vs. 12 (13.8%); $P = 0.018$] and MIOCA cohorts [203 (33.4%) vs. 428 (26.9%); $P = 0.002$]. Age was an independent predictor of MAE in both cohorts. Among MINOCA patients, females ≤ 70 years old had a higher incidence of MAE [18 (23.7%) vs. 4 (5.9%); $P = 0.003$] compared with male peers, mainly driven by a higher rate of re-hospitalization for HF ($P = 0.045$) and recurrence of AMI ($P = 0.006$). Only in this sub-group of MINOCA patients, female sex was an independent predictor of MAE (hazard ratio = 3.09; 95% confidence interval: 1.02–9.59; $P = 0.040$). MINOCA females ≤ 70 years old had worse outcomes than MIOCA female peers.

Conclusion

MINOCA females ≤ 70 years old had a significantly higher incidence of MAE, compared with males and MIOCA female peers, likely due to the different pathophysiology of the ischaemic event.

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She mentioned this because, despite US legislation enacted between 1980 and 1990 that mandated the inclusion of women in clinical trials, women accounted for less than 39% of participants in cardiovascular clinical trials between 2010 and 2017. According to Itchhaporia, this situation limits the potential for developing tailored strategies and recommendations to treat the cardiovascular diseases affecting women..

Emerging Risk Factors

Itchhaporia pointed out that traditional risk factors have been known for many years. For example, 80% of women aged 75 years or younger have arterial hypertension. Only 29% receive adequate blood pressure control, those living with diabetes have a 45% greater risk of suffering ischemic heart disease, and obesity confers a 64% higher risk of developing ischemic heart disease in women vs 46% in men.

In addition to these factors, she noted that emerging factors must be assessed carefully. For example, women who experience pregnancy complications like gestational diabetes have a higher risk for ischemic heart disease and type 2 diabetes. Women with hypertension and preeclampsia are at a threefold higher risk of developing ischemic heart disease.

33. Hypertensive Disorders Screening Recommended for All Pregnant Women

All pregnant women should undergo screening for hypertensive disorders, with evidence-based management for those screening positive, according to a new recommendation from the U.S. Preventive Services Task Force.

Hypertensive disorders of pregnancy in the United States increased from approximately 500 cases per 10,000 deliveries to 1,021 cases per 10,000 deliveries from 1993 to 2016-2017, and remain a leading cause of maternal morbidity and mortality, wrote Task Force Chair Michael J. Barry, MD, of Massachusetts General Hospital, Boston, and colleagues in the final recommendation statement published in JAMA.

The USPSTF commissioned a systematic review to assess the risks and benefits of hypertensive screening for asymptomatic pregnant women. The resulting grade B recommendation indicates that screening for hypertensive disorders in pregnancy using blood pressure measurements yields a substantial net benefit.

The recommendation applies to "all pregnant women and pregnant persons of all genders without a known diagnosis of a hypertensive disorder of pregnancy or chronic hypertension," the authors said.

The recommendation calls for the use of blood pressure measurements to evaluate hypertensive disorders, with measurements taken at each prenatal visit. A positive result for new-onset hypertension was defined as systolic blood pressure of 140 mm Hg or diastolic blood pressure 90 mm Hg in the absence of chronic hypertension, based on two measurements at least 4 hours apart. Regular review of blood pressure can help identify and manage potentially fatal conditions.

However, screening alone is insufficient to improve inequities in health outcomes associated with hypertensive disorders of pregnancy, the authors emphasized. Data from previous studies have shown that Black patients are at increased risk for hypertensive disorders of pregnancy and severe complications, and that Black and Hispanic patients have twice the risk of stroke with hypertensive disorders of pregnancy as White patients.

In the evidence report that supported the recommendation, Jillian T. Henderson, PhD, of Kaiser Permanente in Portland, Ore., and colleagues reviewed six studies including 10,165 individuals. The studies (five clinical trials and one nonrandomized study) compared changes in prenatal screening with usual care.

Overall, the review yielded no evidence that any other screening strategies were more useful than routine blood pressure measurement to identify hypertensive disorders of pregnancy in asymptomatic women.

The findings cited to support the recommendation were limited by several factors, including the lack of power to detect pregnancy health outcomes and potential harms of different screening programs, and the lack of power to evaluate outcomes for American Indian, Alaska Native, or Black individuals, who have disproportionately high rates of hypertensive disorders of pregnancy, the authors said.

34. Upstanders' Needed, Says Practical Guide Tackling Bullying, Harassment

A new practical guide addressing bullying and harassment within the field of cardiology provides actionable recommendations for bystanders, who here have received the new moniker “upstanders.”

It's no secret that the field of cardiology has had issues with hostility in the past, with underrepresented minority groups and women bearing the brunt of the misconduct. What to do about it has been an open question.

“We have moved along from identifying a problem with bullying and harassment,” Renée P. Bullock-Palmer, MD (Deborah Heart and Lung Center, Browns Mills, NJ), the senior author on the new guide, told TCTMD. “The take home message is that if you have been a victim of this or have witnessed this, to really say something. . . and do something about it.”

Writing in the Guest Editor's page in the September 20, 2023, issue of JACC: Case Reports, Katia Bravo-Jaimes, MD (Mayo Clinic, Jacksonville, FL), Bullock-Palmer, and colleagues outline a practical pathway for which they would like to see bullying and harassment in the field addressed.

Notably, they opt to use the term “upstanders” in place of the traditional “bystander.” The goal of doing so was to emphasize the power that a witness can have, even though it can be “intimidating,” according to Bullock-Palmer. Instead of merely being a support person for the victim but keeping quiet, she said that those who observe bullying or harassment should be upstanders by both “saying something to that person and advocating for [them]. If you can, even escalate it to leadership. . . . Being an upstander [can] help to validate their situation.”

The paper also provides definitions for a variety of situations, examining different scenarios within three categories—Bullying and Incivility, Sexism and Gender Disparities, and Microaggressions. Bullock-Palmer highlighted a few, calling out “benevolent sexism” as something that “stems from an often well intended attempt to shield women from perceived harm or hard work, but the decisions or advice that affect them do not consider the will and goals of the woman herself.” One example would be not offering a leadership position to a

woman without even asking her due to the perception that she might be too busy with her family life, Bullock-Palmer explained.

Microaggressions, she said, are also commonly experienced within cardiology. The paper gave the examples of “treating colleagues preferentially based on sexual orientation, ethnicity, or religious preference or even mispronouncing a colleague’s name with no intention to learn the proper way.”

To address these, they suggest using the acronym “ACTION,” which offers a framework for strategies that can be used in the wake of problematic encounters, along with sample:

- Ask clarifying questions
- Curiosity instead of judgement
- Tell the facts you observed
- Intention versus impact
- Own your thoughts, share your reactions
- Next steps

If a witness were to do just one thing in response to bullying or harassment, said Bullock-Palmer, that should be to report the facts of what happened. “Dealing with the situation earlier rather than later is very helpful because sometimes that can impact change, either change in behavior . . . a change in leadership,” she said.

Bullock-Palmer acknowledged that these issues are nothing new, especially in the field of cardiology, and that she has felt discouraged at times. “Unfortunately, change happens very slowly,” she said. “The younger generation gets it, . . . but I think there is that established, engrained male dominance and I think it’s because of that the change has been very slow.

“We’re hoping that the more we speak about it, the more we address it, the more we not only say ‘this is a problem’ but help deal with the problem, will hopefully make the change more impactful,” Bullock-Palmer concluded.