1. Risk of Sports-Related Sudden Cardiac Death in Women

This review article offers a comprehensive overview of the incidence, characteristics, and clinical correlates of sport-related sudden cardiac death (SrSCD) in women vs men. The huge difference in incidence between sexes is the most prominent and consistent information, with male: female ratio in SrSCDs ranging from 7:1 to 32:1. To quote, for example, data from France, the incidence is 0.59–2.17 per million female sports participant-years vs. 11.24–33.84 per million male sports participant-years.\(^1\) Similarly, in the US, the SrSCD incidence in females is 0.66 per million female athlete-years vs 5.01 in males per million male athlete-years.\(^2\)

One may argue that the lower incidence of SrSCD in females is simply consequence of their lower participation in sport activities. However, this hypothesis is easily denied from the actual number of women engaged in sport at all levels: ie, women represented 45% the athlete’s population participating at the recent Olympic Games, and even higher proportion of women are regularly involved in leisure-time athletic activities.

Type of sport (ie, participation in endurance disciplines) and higher intensity of exercise programs have also been postulated as determinants of SrSCD, but this theory clashes with the evidence of the contemporary large participation and high level of achievement of women in the most demanding endurance disciplines, such as marathon running, road cycling, triathlon, or cross-country skiing, where adverse events are reported virtually only in male competitors.

Incidence of SrSCD is largely dependent from the size of population engaged in a certain discipline, with the most popular sports naturally presenting a higher absolute SrSCD rate; in the US, basketball is more commonly associated with SrSCD, whereas in Europe soccer (in males) and then jogging/running, cycling, and swimming are more commonly associated with SrSCD in both sexes.

These data simply confirm that sport is not, per se, the cause of SrSCD, but only the trigger of the event in presence of an underlying, cardiac disease. Accordingly, the previous literature has extensively reported the most common pathologic conditions associated with sudden death, such as cardiomyopathies, (eg, hypertrophic or arrhythmogenic cardiomyopathy), coronary artery disease or channelopathies (eg, long QT syndrome, early repolarization, catecholaminergic ventricular tachycardia).

Well, even in the presence of a known pathologic substrate, women seem to have less proclivity than men for developing ominous ventricular arrhythmias. For instance, in patients with HCM, exercise-induced ventricular arrhythmias are reported more commonly in men than in women. Similarly, more men experience malignant arrhythmias in dilated cardiomyopathy and arrhythmogenic cardiomyopathy.\(^3\)

The different hormonal environment may explain part of these differences; when an arrhythmogenic substrate is present, elevated testosterone levels, as well as lower oestradiol levels, are associated with higher risk of malignant ventricular arrhythmias.

Indeed, proportion of HCM in the French registry accounted for only 14% of female SrSCDs vs 51% of male SrSCDs.\(^1\) Overall, in the same registry 42% of SrSCDs in women were nonstructural, vs 4% in men, suggesting that the largest proportion of SrSCD in women have a normal cardiac pathologic examen.
The role of doping agents and drugs of common use (antidepressant, stimulants) remains to be fully elucidated. Anabolic androgenic steroids are associated with cardiac hypertrophy, arrhythmias, and SCD. Multiple studies showed that women were less likely than men to use anabolic steroids placing them at lower risk. Finally, social or behavioral differences between the genders, eg, a proclivity for men to use performance-enhancing drugs or overexert, could also contribute to the dissimilarity in SrSCD incidence.

Take-home message: The review article confirms the huge difference of Sr SCD among sexes and delineates the potential mechanisms protecting women’s hearts. The available information is still incomplete and further studies are needed to uncover the mechanisms by how SrSCD can be prevented.

2. Maternal Cardiac Function at Midgestation and Development of Preeclampsia

Background

Preeclampsia (PE) is an independent risk factor for adverse maternal cardiovascular outcomes. The role of maternal cardiac function in the pathophysiology of PE remains unclear.

Objectives

This study sought to describe differences in cardiac function at midgestation between women who develop PE and those with uncomplicated pregnancy and to establish whether routine cardiac assessment at midgestation can improve performance of screening for PE achieved by established biomarkers.

Methods

Mean arterial pressure was measured, medical history was obtained, and left ventricular (LV) systolic and diastolic functions were assessed using standard echocardiography and speckle tracking imaging. Uterine artery pulsatility index and serum placental growth factor and soluble fms-like tyrosine kinase-1 were measured.

Results

In 4,795 pregnancies, 126 (2.6%) developed PE. Following multivariable analysis, peripheral vascular resistance was significantly higher and LV global longitudinal systolic strain, ejection fraction, cardiac output, and left atrial area were mildly lower in women who developed PE compared to those who did not. There was a weak association between maternal cardiovascular indices and biomarkers of placental perfusion and function. Cardiac indices did not improve the performance of screening for PE on top of maternal risk factors, mean arterial pressure, and biomarkers of placental perfusion and function.

Conclusion

Women who develop PE have an increase in peripheral vascular resistance and a mild reduction in LV functional cardiac indices long before PE development. However, cardiac indices do not improve the performance of screening for PE; thus, their routine clinical use is not advocated.

3. Sex matters? Sex matters!
Improved understanding of the development and prevention of coronary artery diseases has led to a >60% reduction in deaths from heart attack and stroke over the past four decades; however, alarmingly, the lowest rate of improvement over the past 20 years has been in younger women. Retrospective analyses of previous basic research studies, clinical trials, and care management have taught us that major bias has been introduced by focusing attention on male subjects, particularly in research into cardiovascular disorders. We observed that mortality in women (<50 years old) in the context of myocardial infarction was twice that in men. The causes of this discrepancy are multiple and include under-diagnosis of women, as well as less frequent administration of (appropriate) drugs and use of relatively fewer invasive exams or therapies. Delay in care management and shorter stay in intensive care units are also more common for women than men. Although this sex gap is increasingly recognized in research, it has yet to be fully addressed, as stratification of data by sex remains uncommon.

Further, differences in the clinical presentation must also be considered (e.g. sex differences in non-obstructive coronary artery disease), not only in clinical management but also in clinical trial inclusion criteria. Indeed, the participation of women in clinical trials on cardiovascular disease is often not representative of the female: male ratio of those affected by the condition under study. This imbalance is also observed at the preclinical stage, with a poorly justified favouring of male over female animal models. Discovery of biomarkers or results obtained from investigations focused on males is not necessarily transferable to females. Aside from sex differences, the age of women enrolled in clinical trials often biases drug safety and efficacy data.

Given this regrettable situation, Bernabeu et al. took advantage of the UK Biobank resources to study the existence and the scope of genotype by sex among more than 450 000 individuals (245 000 females and 205 000 males) from the general population and for 446 binary (defined as trait with only two possible values such as ‘heart attack/myocardial infarction’ YES/NO or ‘Cardiomyopathy’ YES/NO) and 84 non-binary traits (such as quantitative traits or percentage values ‘Alcohol intake frequency’ or ‘Trunk fat percentage’, respectively). They then tested whether the genetic architecture of traits may differ according to sex and include potential sex-specific biomarkers. In the recent publication of their study in Nature Genetics, the authors navigate away from the expected paradigm by investigating whether genetic background contributes to traits that differ between the sexes.

First, they measured genetic heritability (the fraction of a trait explained by the combination of common genetic variants; Figure 1). Surprisingly, approximately 50% of binary and 7% of non-binary traits exhibited significant differences between the sexes, indicating that genetic variants underlying susceptibility or modulation of 71 traits differed between male and female or were absent in one sex; among these, non-binary phenotypes were body mass-associated traits, while binary phenotypes included ankylosing spondylitis, disorders of mineral metabolism, and soft-tissue disorders. Interestingly, of identified differences in heritability, few were due to environmental variance, supporting a role for genetic variation in the observed sex differences in heritability. Consistent with these findings, an absence in genetic correlation between males and females was detected for 69 traits, indicating genetic heterogeneity. Interestingly, the majority of sex-specific markers were on autosomes, while the X-chromosome appeared to explain only a small proportion (on average) of sex-specific genetic heritability.

To decipher genetic differences at the nucleotide (single nucleotide polymorphism; SNP) level, sex-dimorphic SNPs (sdSNP) between males and females were subsequently called and sex-stratified genome-wide association studies conducted. More than 8200 sdSNPs on autosomes
showed evidence of a specific sex-associated variant. These SNPs corresponded to 264 and 88 independent loci associated with non-binary and binary traits, respectively. Further, 37 sdSNPs and 8 unique loci were identified on the X-chromosome. Traits associated with the largest number of sdSNPs spread across the autosomes were for 'waist: hip circumference ratio', with 'hematocrit percentage' identified as associated with X-chromosome-associated sdSNPs.

As a proof of concept for potential future guidelines, Bernabeu et al. evaluated the number of genetic variants that may be ignored by sex-agnostic analyses. Indeed, the ability to identify an associated variant may be masked by differences in effect size, or even direction, in one of the sexes, when a sex-agnostic analytic approach is applied (Figure 1). Among the 530 traits studied, 22% of binary and 93% of non-binary traits had at least one variant that showed this masking effect. Examples of variants with opposite effects are also reported, although these represent a small proportion. These results underline the need to stratify analysis, as well as ensuring balanced male/female inclusion, to avoid false-positive results due to sample size differences.

As a perspective, the results reported by Bernabeu et al. are encouraging with regard to the possibility of improving cardiovascular phenotype prediction based on sex-specific genetic models. The authors provide evidence based-genetics that will help us to tackle our preconceptions and contribute to re-thinking research study design and data interpretation approaches. Indeed, the time has come to the end of the restriction of research, clinical trials, and clinical management to simplistic sex-agnostic designs. The take home message of this study also lies in the possibility for retrospective analysis of previous investigations focused on the sex-agnostic model, likely including a majority of the 1600 cardiovascular traits associated with
genetic loci (according the GWAS catalogue). Bernabeu et al. have made a definitive contribution to the development of personalized preventive medicine, where the genetic specificity of disease susceptibility in both females and males is considered.

4. Ending Gender Inequality in Cardiovascular Clinical Trial Leadership: JACC Review Topic of the Week

Women are under-represented as leaders of cardiovascular randomized controlled trials, representing 1 in 10 lead authors of cardiovascular trials published in high-impact journals. Although the proportion of cardiovascular specialists who are women has increased in recent years, the proportion of cardiovascular clinical trialists who are women has not. This gap, underpinned by systemic sexism, has not been adequately addressed. The benefits of diverse randomized controlled trial leadership extend to patients and professionals. In this position statement, we present strategies adopted by some organizations to end gender inequality in research leadership. We offer an actionable roadmap for early-career researchers, scientists, academic institutions, professional societies, trial sponsors, and journals to follow, with the goal of harnessing the strength of women and under-represented groups as research leaders and facilitating a just culture in the cardiovascular clinical trial enterprise.

Highlights

• Women are under-represented in the leadership of high-profile, multicenter cardiovascular clinical trials.

• Diversity in clinical trial leadership is associated with more diverse trial participants, which improves the generalizability of results and analysis of treatment interactions.

• Systemic sexism must be overcome to enhance the representation of women in cardiovascular practice and trial leadership.

• Deliberate action and monitoring of key metrics by individual investigators, academic institutions, professional societies, industry sponsors, funding agencies, and scientific journals are needed to overcome gender inequalities in cardiovascular clinical trial leadership.

5. Social Determinants of Suboptimal Cardiovascular Health Among Pregnant Women in the United States


**Background**

Suboptimal cardiovascular health (CVH) and social determinants of health (SDOH) have a significant impact on maternal morbidity and mortality. We aimed to evaluate the association of SDOH with suboptimal CVH among pregnant women in the United States.

**Methods and Results**

We examined cross-sectional data of pregnant women aged 18 to 49 years from the National Health Interview Survey (2013–2017). We ascertained optimal and suboptimal CVH based on the presence of 0 to 1 and ≥2 risk factors (hypertension, diabetes, hyperlipidemia, current smoking, obesity, and insufficient physical activity), respectively. We calculated an aggregate SDOH score representing 38 variables from 6 domains (economic stability; neighborhood, physical environment, and social cohesion; community and social context; food; education; and healthcare system) and divided into quartiles. We used Poisson regression model to evaluate the association of SDOH with suboptimal CVH and risk factors. Our study included 1433 pregnant women (28.8±5.5 years, 13% non-Hispanic Black). Overall, 38.4% (95% CI, 33.9–43.0) had suboptimal CVH versus 51.7% (95% CI, 47.0–56.3) among those in the fourth SDOH quartile. Risk ratios of suboptimal CVH, smoking, obesity, and insufficient physical activity were 2.05 (95% CI, 1.46–2.88), 8.37 (95% CI, 3.00–23.43), 1.54 (95% CI, 1.17–2.03), and 1.19 (95% CI, 1.01–1.42), respectively among those in the fourth SDOH quartile compared with the first quartile.

**Conclusions**

Over 50% of pregnant women with the highest SDOH burden had suboptimal CVH, highlighting the public health urgency for interventions in socially disadvantaged pregnant women with renewed strategies toward improving modifiable risk factors, especially smoking and insufficient physical activity.

**6. Breastfeeding reduces mothers’ cardiovascular disease risk**

The special issue, JAHA Spotlight on Pregnancy and Its Impact on Maternal and Offspring Cardiovascular Health, includes about a dozen research articles exploring various cardiovascular considerations during pregnancy for mother and child.

The health benefits of breastfeeding for children are well known. According to the World Health Organization (WHO), it is linked with fewer respiratory infections and lower risk of death from infectious diseases among the children who were breastfed. Breastfeeding also has been linked to maternal health benefits, including lower risk for Type 2 diabetes, ovarian cancer and breast cancer.

"Previous studies have investigated the association between breastfeeding and the risk of cardiovascular disease in the mother; however, the findings were inconsistent on the strength of the association and, specifically, the relationship between different durations of breastfeeding and cardiovascular disease risk. Therefore, it was important to systematically review the available literature and mathematically combine all of the evidence on this topic," said senior author Peter Willeit, M.D., M.Phil., Ph.D., professor of clinical epidemiology at the Medical University of Innsbruck in Innsbruck, Austria.
Researchers reviewed health information from eight studies conducted between 1986 and 2009 in Australia, China, Norway, Japan and the U.S. and one multinational study.

The review included health records for nearly 1.2 million women (average age 25 at first birth) and analyzed the relationship between breastfeeding and the mother’s individual cardiovascular risk.

"We collected information, for instance, on how long women had breastfed during their lifetime, the number of births, age at first birth and whether women had a heart attack or a stroke later in life or not," said first author Lena Tschiderer, Ph.D., a postdoctoral researcher at the Medical University of Innsbruck.

The review found:

- 82% of the women reported they had breastfed at some time in their life.
- Compared to women who never breastfed, women who reported breastfeeding during their lifetime had a 11% decreased risk of developing cardiovascular disease.
- Over an average follow-up period of 10 years, women who breastfed at some time in their life were 14% less likely to develop coronary heart disease; 12% less likely to suffer strokes; and 17% less likely to die from cardiovascular disease.
- Women who breastfed for 12 months or longer during their lifetime appeared to be less likely to develop cardiovascular disease than women who did not breastfeed.
- There were no notable differences in cardiovascular disease risk among women of different ages or according to the number of pregnancies.

Despite recommendations to breastfeed by organizations including the WHO and the U.S. Centers for Disease Control and Prevention (CDC), both of which recommend babies are breastfed exclusively through at least six months of age, only 1 in 4 infants receives only breastmilk for the first six months of life. Black infants in the U.S. are less likely than white infants to be breastfed for any length of time, according to the CDC.

"It's important for women to be aware of the benefits of breastfeeding for their babies' health and also their own personal health," Willeit said. "Moreover, these findings from high-quality studies conducted around the world highlight the need to encourage and support breastfeeding, such as breastfeeding-friendly work environments, and breastfeeding education and programs for families before and after giving birth."

The U.S. has the highest maternal death rate among developed countries, and cardiovascular disease is the leading cause, according to the 2021 Call to Action Maternal Health and Saving Mothers policy statement from the American Heart Association. The statement, which outlines public policies that address the racial and ethnic disparities in maternal health, notes that an estimated 2 out of 3 deaths during pregnancy may be preventable.

"While the benefits of breastfeeding for infants and children are well established, mothers should be further encouraged to breastfeed their infants knowing that they are improving the health of their child and improving their own health as well," said Shelley Miyamoto, M.D., FAHA, chair of the American Heart Association’s Council on Lifelong Congenital Heart Disease and Heart Health
in the Young (Young Hearts), the Jack Cooper Millisor Chair in Pediatric Heart Disease and director of the Cardiomyopathy Program at Children's Hospital Colorado in Aurora. "Raising awareness regarding the multifaceted benefits of breastfeeding could be particularly helpful to those mothers who are debating breast vs. bottle feeding.

"It should be particularly empowering for a mother to know that by breastfeeding she is providing the optimal nutrition for her baby while simultaneously lowering her personal risk of heart disease."

A limitation of this meta-analysis is that little information was available about women who breastfed for longer than two years. "If we had this additional data, we would have been able to calculate better estimates for the association between lifetime durations of breastfeeding and development of cardiovascular disease in mothers," Tschiderer said.

7. Racialised people in clinical guideline panels

Clinical practice guidelines can include recommendations with important implications for health equity; therefore, guideline panels should comprise individuals positioned to make relevant recommendations, including those that reflect the diversity of the priority population.

Women are under-represented in guideline panels, and, although the inclusion of racialised people in guideline panels has received less attention, racialised clinicians are discriminated against in training and hiring.

We determined the extent to which guideline panels included racialised people and women.

We included all clinical practice guidelines published in national general medical journals from Australia, Canada, the UK, and the USA between June, 2014, and June, 2021, by searching MEDLINE and websites of the British Medical Journal (BMJ), Canadian Medical Association Journal (CMAJ), Medical Journal of Australia (MJA), and JAMA. Two research team members (two of MA, HW, and AW) extracted data from each guideline including the guideline panel membership. We defined guideline panel members as individuals who were involved in drafting recommendations.

We determined whether each guideline panel member was a white person (binary: racialised or not racialised) and their gender (categorical: identifies as a woman, identifies as a man, or non-binary) by reviewing the panel member's name and pronoun if available, and their institutional profile, and by conducting internet searches (eg, Wikipedia). Two research team members (two of MA, HW, and AW) independently performed the assessment for each guideline panel member and a third member (one of MA, HW, AW, and NP) helped resolve disagreements. We validated our method by contacting a random sample of 100 guideline panel members by email asking them to indicate their gender and racialisation, and using the Onomap algorithm, which identifies ethnicity on the basis of names (appendix pp 3–5, 7).

The study was approved by the Research Ethics Board of Unity Health Toronto.
1184 records were identified and 237 guidelines were included. Guidelines or guideline summaries were published in the MJA (53 [22%] of 237), JAMA (28 [12%]), BMJ (35 [15%]), CMAJ (30 [13%]), Circulation (seven [3%]), and other journals (84 [35%]).

The 237 guidelines involved 3696 unique guideline panel members (figure). Of these, 1396 (38% [margin of error 2%]) of 3696 were women, 2225 (60% [2%]) were men, and gender was unclear for 75 (2% [2%]; appendix p 9). There were 750 (20% [2%]) racialised guideline panel members, 2723 (74% [2%]) white guideline panel members, and racialisation status was unclear for 223 (6% [2%]) members. 271 (7% [2%]) racialised guideline panel members were women. Guideline panels included a median of 14 (IQR 10–19) members. Panels included a median of five (3–8) women, nine (5–11) men, a median of two (1–4) racialised members and 11 (7–14) white members. 92 (39%) of the 237 panels did not include any racialised women, 83 (35%) included one, 31 (13%) included two, and 27 (11%) included three to five women. Virtually all (231 [97%]) panels included at least one white man, ten (4%) included only one white man, 18 (8%) included two, and 23 (10%) included three, whereas most panels (180 [76%]) included four or more white men. The results were similar across jurisdictions; the most common category of panel member was white men and the least common was racialised women 67 (28%) of 237 guidelines either did not mention the selection process or included a non-informative declaration that the panel was formed (eg, “a working group was formed”). 60 (25%) of 237 guidelines referred to another organisation, such as a medical society, without explaining how panel members were identified. Most guideline publications (131 [55%] of 237) did not mention gender or race in the recommendations or supporting text. Panel composition did not substantially differ between those that did and did not mention gender or race as both had a median of five (IQR 3–7) women and a median of two (1–4) racialised panel members.

Our findings that guideline panels included more white people than racialised people, and that racialised women were often not included, accords with previous evidence of structural racism and racial disparities at various levels within academic medicine.

Intersectionality is a framework that underscores the complexity of intersecting social factors and their interaction with compounding power structures and discrimination; our findings can be explored via this lens given that most guideline panels exclude racialised women.

To our knowledge, this is the first study of the inclusion of racialised individuals in practice guidelines panels. We determined racialisation status based on information publicly available about guideline panel members, including pictures and academic profiles; the same type of information that can be used to discriminate against an individual. Some categorisations could have been inaccurate, although there was high inter-rater agreement, and we validated our approach against self-reports and an algorithm for determining ethnicity.

A first step towards appropriate and fair guideline panels could be to update guidance for guideline makers and evaluators such as the Appraisal of Guidelines, Research and Evaluation (AGREE II) reporting checklist, and Reporting Items for practice Guidelines in HealthCare (RIGHT) to promote the reporting of panel selection processes.

Guideline funders and journals that publish guidelines could insist on explanations of why racialised people and women were not included. Transparency about selection processes—and specifically how equity is addressed in the selection process—might help identify needed changes that could be implemented immediately.
8. Race, Income Remain Predictors of Acute MI Revascularization in Women

Despite better awareness and focused initiatives, Black race and lower income are still associated with a lower likelihood of receiving coronary revascularization among postmenopausal women presenting with acute MI, according to an analysis of the Women’s Health Initiative study.

The data demonstrate long-identified problems, senior author Khadijah Breathett, MD (University of Arizona, Tucson), told TCTMD. “We all know women are less likely to receive appropriate care for cardiovascular treatment, and this shows that it’s that much worse for Black women or for women with lower income,” she said.

But given the recent “increased awareness” of these issues and the drive to eliminate health disparities by various policies and programs, this study was designed to see if these efforts have made any difference, said lead author Tarryn Tertulien, MD (University of Pittsburgh Medical Center, PA).

The results, published online last week ahead of print in the American Heart Journal, show in a population of more than 5,200 people presenting with acute MI over several decades that Black versus white patients were less likely to receive coronary revascularization (adjusted HR 0.79; 95% CI 0.66-0.95), as were those with annual incomes under versus over $20,000 (adjusted HR 0.90; 95% CI 0.82-0.99).

While the size of the observed disparities surprised her, Tertulien said, “it’s a slow process in terms of really improving, for example, risk factors such as access to care [and] physical activity. . . . I think it might take a bit longer to see differences.” Further, the data don’t suggest that public health initiatives like Healthy People 2010 did not have an overall impact, she added.

Commenting on the results for TCTMD, Erin D. Michos, MD (Johns Hopkins University School of Medicine, Baltimore, MD), said it was “disheartening” to see that racial disparities in revascularization access for acute MI have not improved over time. “I would have thought that maybe things would have been better in the more recent era,” she said in an email.

“Race is a social construct rather than a genetic/biologic construct,” Michos continued. “These persistent racial disparities across trials are likely due to social inequities, reduced access to care, and other disparate treatment that can stem from systemic racism. This is really unacceptable and needs to change immediately.”

Disparities Persist

For the analysis, Tertulien and colleagues included data from the Women’s Health Initiative on 5,284 postmenopausal women (mean age 66.3 years; 9.5% Black, 2.8% Hispanic, 87.7% white; 23.2% with annual incomes < $20,000) presenting with acute MI between 1993 and 2019.
We all know women are less likely to receive appropriate care for cardiovascular treatment, and this shows that it's that much worse for Black women or for women with lower income. Khadijah Breathett

While the prevalence of coronary heart disease was similar across racial, ethnic, and income groups, Black women and women with lower incomes had higher proportions of diabetes and hypertension and less physical activity than white women and those with higher incomes. Heart failure was also more prevalent among Black women.

After adjustment, coronary revascularization was less often performed in Black versus white patients but was similarly offered to Hispanic and white women (adjusted HR 1.07; 95% CI 0.82-1.38).

Specifically, Black women were less likely to receive PCI compared with white women (adjusted HR 0.72; 95% CI 0.59-0.90) but similarly offered CABG irrespective of STEMI or NSTEMI presentation. There was no difference in receipt of revascularization type by income.

The researchers noted a steady increase in revascularization between 2005 and 2019 overall, but the racial disparities remained. In fact, in subanalyses looking at before and after 2010, there were still significant racial differences in coronary revascularization.

**Standardization, Antiracist Trainings Needed**

Tertulien said she hopes these data will increase the importance of recognizing how social determinants of health can affect care for patients with acute MI. She called for more-inclusive studies to address these issues as well as structural racism.

Additionally, Breathett said more standardization “will really start to go a long way.” While the recently updated chest pain and revascularization guidelines “may play a large role,” the entire process of care for these patients needs more standardization, she said. “It can’t be based upon the patient’s race or income. Oftentimes misjudgment of adherence levels and ability to return for follow-up should not impact [decisions] about the patient’s care. It should be focused on how to address the issues that are contributing to the initial disease presentation.”

**This is really unacceptable and needs to change immediately.** Erin D. Michos

Michos agreed. “We have established guidelines, but the implementation piece is often lacking,” she said. “We need more implementation science to understand best strategies of how to deliver appropriate guideline-recommended therapies, which include revascularization for acute MI as well as preventive medications such as statins.”

Moreover, Breathett said antiracist and evidence-based bias reduction training should be mandatory for entire institutions and policies should be assessed for their impact on patients based on race, ethnicity, sex, and age. “We know this is a problem across cardiovascular care with the differences in who receives guideline-directed treatment, but it has to be a standard that hospitals have to be willing to step up to,” she said. “And we also must charge the insurance companies to prevent the barriers for allowing the patients to get the medications and the treatment that they need. So it’s a major systemic problem that requires a systemic solution.”
Even so, Breathett said she anticipates that change is coming. “Leaders are starting to listen, Institutions care about what's happening to our patients, and I hope that [due to] continued pressure to recognize that we cannot afford to allow for these disparities to persist that change will start to come and equity will become a true priority,” she said.


BACKGROUND
We aimed to address which antihypertensives are superior to placebo/no therapy or another antihypertensive for controlling nonsevere pregnancy hypertension and provide future sample size estimates for definitive evidence.

METHODS
Randomized trials of antihypertensives for nonsevere pregnancy hypertension were identified from online electronic databases, to February 28, 2021 (registration URL: https://www.crd.york.ac.uk/PROSPERO/; unique identifier: CRD42020188725). Our outcomes were severe hypertension, proteinuria/preeclampsia, fetal/newborn death, small-for-gestational age infants, preterm birth, and admission to neonatal care. A Bayesian random-effects model generated estimates of direct and indirect treatment comparisons. Trial sequential analysis informed future trials needed.

RESULTS
Of 1246 publications identified, 72 trials were included; 61 (6923 women) were informative. All commonly prescribed antihypertensives (labetalol, other β-blockers, methyldopa, calcium channel blockers, and mixed/multi-drug therapy) versus placebo/no therapy reduced the risk of severe hypertension by 30% to 70%. Labetalol decreased proteinuria/preeclampsia (odds ratio, 0.73 [95% credible interval, 0.54–0.99]) and fetal/newborn death (odds ratio, 0.54 [0.30–0.98]) compared with placebo/no therapy, and proteinuria/preeclampsia compared with methyldopa (odds ratio, 0.66 [0.44–0.99]) and calcium channel blockers (odds ratio, 0.63 [0.41–0.96]). No other differences were identified, but credible intervals were wide. Trial sequential analysis indicated that 2500 to 10 000 women/arm (severe hypertension or safety outcomes) to >15 000/arm (fetal/newborn death) would be required to provide definitive evidence.

CONCLUSIONS
In summary, all commonly prescribed antihypertensives in pregnancy reduce the risk of severe hypertension, but labetalol may also decrease proteinuria/preeclampsia and fetal/newborn
10. **Policy Change Needed to Improve Maternal Cardiovascular Health**

During the past 4 decades, the number of women dying during pregnancy or within the first year after childbirth has increased significantly. Our nation loses about 2 women every day—700 women a year—to childbirth, an annual death toll in the United States that has doubled since the late 1980s, despite steep declines elsewhere in global maternal mortality rates during the same period.\(^1\) In addition, 10% to 15% of women experience pregnancy complications (adverse pregnancy outcomes), including hypertensive disorders of pregnancy (high blood pressure), gestational diabetes, preterm delivery, small-for-gestational-age delivery, pregnancy loss, or placental abruption, increasing a woman’s risk for developing cardiovascular disease (CVD) later in life.

Pregnancy causes significant clinical effects on physical and emotional health. Patient-centered coordinated care models have developed over the years to improve patient outcomes, yet many expectant and new mothers still lack sufficient health care during their life course. The paradigm and policy solutions for how we care for women in their reproductive years from long before pregnancy to well after childbirth need to evolve and improve with a focus on addressing systemic inequities, as disparities in health and health care access already exist by the time women enter their reproductive years. Following clinical guidance on maternal cardiovascular health, the American Heart Association recently published the policy statement “Call to Action: Maternal Health and Saving Mothers,” which details 8 key strategies to shift the maternal health paradigm and save lives as outlined in the Figure.\(^2\) These recommendations address factors influencing maternal outcomes before, during, and after pregnancy, and represent the American Heart Association’s commitment to advocating for solutions that will equitably improve maternal health at the population level.

![Figure](image)

**Figure.** **Multipronged approach to achieving sustainable maternal health equity.** IT indicates information technology.

Increasing access to public and private health insurance coverage and enhancing access to quality, affordable, patient-centered care for every person living in the United States provides an...
opportunity to improve cardiovascular and maternal outcomes for pregnant individuals. Women with underlying cardiovascular disease before pregnancy are at increased risk for cardiac events during pregnancy and in the postpartum period. These women should be screened with the World Health Organization risk assessment tool before they conceive and have a shared decision-making discussion with the obstetrician and cardiologist regarding pregnancy risks, close monitoring, and personalized care during the peripartum period.

Pregnancy is considered a physiological stress test and may unmask previously unrecognized CVD during pregnancy. Furthermore, women with hypertension, diabetes, dyslipidemia, or obesity, sedentary lifestyle, and history of or current tobacco use are at risk for developing adverse pregnancy outcomes, which in turn increases their lifetime risk of developing atherosclerotic CVD, hypertension, hemorrhagic stroke, and heart failure. Preeclampsia is a more severe type of hypertensive disorder of pregnancy and although it is an obstetric emergency, it also has significant latent cardiovascular effects. Women with preeclampsia have a 2-fold increased risk for developing coronary heart disease, stroke, and CVD or CVD mortality, and are at higher risk during the first 10 years after pregnancy (compared with beyond 10 years). Racial and ethnic differences exist in terms of CVD risk factors and maternal mortality. Pregnancy-related mortality rates are up to 2 to 3 times higher in non-Hispanic Black and American Indian/Alaska Native women than in White women.

Promoting and integrating preconception counseling into the regular care of women during their reproductive years is integral to mitigating disparities in outcomes and preventing the development of serious health complications in pregnancy. Although CVD is the leading cause of maternal mortality, most women who die of CVD-related pregnancy complications have no previous diagnosis of CVD. Incorporating screening for CVD and its major risk factors earlier in women's health care, and specifically within family planning conversations and practices, will improve a provider's ability to maximize their patients’ opportunities for healthy pregnancies and positive birth outcomes.

The American Heart Association is already following through with advocacy initiatives to achieve these strategies.

**Cultural Norms and Diverse Perspectives**

Addressing inequities and structural racism that lead to disparities in maternal care and outcomes requires intentional effort to reduce bias and advance cultural awareness across the health system, especially in reproductive health.

The recruitment and retention of a diverse workforce with the ability to provide culturally and linguistically appropriate care is critical to addressing disparities in maternal care. In alignment with an organizational commitment to advance diversity among health care professionals, the American Heart Association has recently expanded its Black and Hispanic Scholars Programs at Historically Black Colleges and Universities and Hispanic-Serving Institutions to enhance the pipeline of individuals entering health care from diverse backgrounds. These pipeline programs are critical in developing a diverse health care workforce that can respond in culturally sensitive ways and engage in early interventions.

There is also a need to educate women on the early warning signs of maternal morbidity, in addition to when urgent action is needed. These and other efforts to improve the maternal health
paradigm must extend beyond the health system to involve families and our communities to ensure all mothers not just survive, but thrive.

**What is Currently Happening at the State and Federal Level**

Among the American Heart Association’s top advocacy priorities is the expansion of Medicaid in all 50 states and extending postpartum Medicaid coverage from 60 days to a full year to ensure the continuity of care for individuals experiencing pregnancy. In recent months, several states have applied for Section 1115 waivers from the Centers for Medicare and Medicaid Services to extend postpartum Medicaid coverage, with New Jersey becoming the fourth state to have its waiver approved in October 2021. As an example of this action, more than 8700 postpartum New Jersey residents each year will be able to remain covered by Medicaid in the 12 months after giving birth, demonstrating the enormous effect of these and similar efforts in other states in supporting the health of women by preventing dangerous lapses in coverage and expanding access to comprehensive health care. The federal American Rescue Plan Act was signed into law in March 2021, taking a critical step toward birth equity by creating another temporary pathway for states to extend Medicaid coverage from 60 days to 12 months postpartum. This state plan option expires after 5 years, necessitating additional action to make such a pathway permanent.

There has been significant effort under the present administration to advance maternal health and inject equity into the provision and evaluation of maternal care. These include efforts to permanently extend postpartum Medicaid coverage to 12 months, end racial and ethnic disparities in birthing outcomes, address social determinants of maternal health, and grow and diversify the perinatal health workforce. In addition, there are several bipartisan bills being considered in the Senate and House of Representatives to equitably improve maternal health, including policies to enhance data collection and quality measures, promote new payment models, and expand access to digital tools. The American Heart Association looks forward to exploring opportunities to work with Congress, as well as present and future administrations, to advance these priorities.

**Conclusions**

The American Heart Association is committed to supporting policy, system, and community-level changes that will enhance maternal health in the United States and across the globe and will continue advocating for these changes and hope health care providers, policy makers, and patients will do so as well.

11. **Genes That Escape X Chromosome Inactivation Modulate Sex Differences in Valve Myofibroblasts**

Background:
Aortic valve stenosis is a sexually dimorphic disease, with women often presenting with sustained fibrosis and men with more extensive calcification. However, the intracellular molecular mechanisms that drive these clinically important sex differences remain underexplored.

Methods:

Hydrogel biomaterials were designed to recapitulate key aspects of the valve tissue microenvironment and to serve as a culture platform for sex-specific valvular interstitial cells (VICs; precursors to profibrotic myofibroblasts). The hydrogel culture system was used to interrogate intracellular pathways involved in sex-dependent VIC-to-myofibroblast activation and deactivation. RNA sequencing was used to define pathways involved in driving sex-dependent activation. Interventions with small molecule inhibitors and siRNA transfections were performed to provide mechanistic insight into sex-specific cellular responses to microenvironmental cues, including matrix stiffness and exogenously delivered biochemical factors.

Results:

In both healthy porcine and human aortic valves, female leaflets had higher baseline activation of the myofibroblast marker α-smooth muscle actin compared with male leaflets. When isolated and cultured, female porcine and human VICs had higher levels of basal α-smooth muscle actin stress fibers that further increased in response to the hydrogel matrix stiffness, both of which were higher than in male VICs. A transcriptomic analysis of male and female porcine VICs revealed Rho-associated protein kinase signaling as a potential driver of this sex-dependent myofibroblast activation. Furthermore, we found that genes that escape X-chromosome inactivation such as BMX and STS (encoding for Bmx nonreceptor tyrosine kinase and steroid sulfatase, respectively) partially regulate the elevated female myofibroblast activation through Rho-associated protein kinase signaling. This finding was confirmed by treating male and female VICs with endothelin-1 and plasminogen activator inhibitor-1, factors that are secreted by endothelial cells and known to drive myofibroblast activation through Rho-associated protein kinase signaling.

Conclusions:

Together, in vivo and in vitro results confirm sex dependencies in myofibroblast activation pathways and implicate genes that escape X-chromosome inactivation in regulating sex differences in myofibroblast activation and subsequent aortic valve stenosis progression. Our results underscore the importance of considering sex as a biological variable to understand the molecular mechanisms of aortic valve stenosis and to help guide sex-based precision therapies.

12. **Arrhythmias in Pregnancy**

Increasing maternal mortality and incidence of arrhythmias in pregnancy have been noted over the past 2 decades in the United States. Pregnancy is associated with a greater risk of arrhythmias, and patients with a history of arrhythmias are at significant risk of arrhythmia recurrence during pregnancy. The incidence of atrial fibrillation in pregnancy is rising. This
review discusses the management of tachyarrhythmias and bradyarrhythmias in pregnancy, including management of cardiac arrest. Management of fetal arrhythmias are also reviewed. For patients without structural heart disease, β-blocker therapy, especially propranolol and metoprolol, and antiarrhythmic drugs, such as flecainide and sotalol, can be safely used to treat tachyarrhythmias. As a last resort, catheter ablation with minimal fluoroscopy can be performed. Device implantation can be safely performed with minimal fluoroscopy and under echocardiographic or ultrasound guidance in patients with clear indications for devices during pregnancy. Because of rising maternal mortality in the United States, which is partly driven by increasing maternal age and comorbidities, a multidisciplinary and/or integrative approach to arrhythmia management from the prepartum to the postpartum period is needed.