# May Monthly News 2024

## 1. Impact of female sexual dysfunction on cardiovascular diseases

Dyslipidaemia, diabetes, hypertension, smoking, abdominal obesity, and daily physical activity are recognized as crucial cardiovascular risk factors across all genders and ages.1–4 Recent findings highlight that the comprehensive management of multiple cardiovascular risk factors in patients at high risk remains inadequate globally. The inability to manage a single risk factor often correlates with poor control over other risk factors.5 Moreover, the interplay of several elements, including adherence to medication, physical activity, and smoking habits, significantly influences the success of risk factor management. Additionally, healthcare system-related factors (e.g. medication accessibility or reimbursement, public awareness of cardiovascular diseases and their risk factors, and adequate physician support and follow-up) and physician-related factors (e.g. accurate risk assessment and medication optimization for patients not achieving target goals) play pivotal roles in achieving desired outcomes.5

Obesity is a known contributor to cardiovascular disease risk in both genders; however, its clinical prevalence and impact on key cardiovascular risk factors vary by gender. The mechanisms through which obesity exacerbates cardiovascular risk differ significantly among women during their pre-menopausal, pregnancy, and post-menopausal stages.6 Regardless of reproductive status or age, the manifestation of cardiovascular events in obese women is closely linked with hypertension and its subsequent chronic complication, heart failure with preserved ejection fraction.6 Obesity also heightens the risk of both hypertension and heart failure during pregnancy.6 Female cardiovascular risk factors have been broadly classified into those specific to females (reproductive, pregnancy, menopausal) and those predominant in females (depression, exposure

to anthracyclines, autoimmune diseases).7 Research on female sex-specific cardiovascular risk factors has focused on oral contraceptive use, menopausal status, and hormone replacement therapy.7

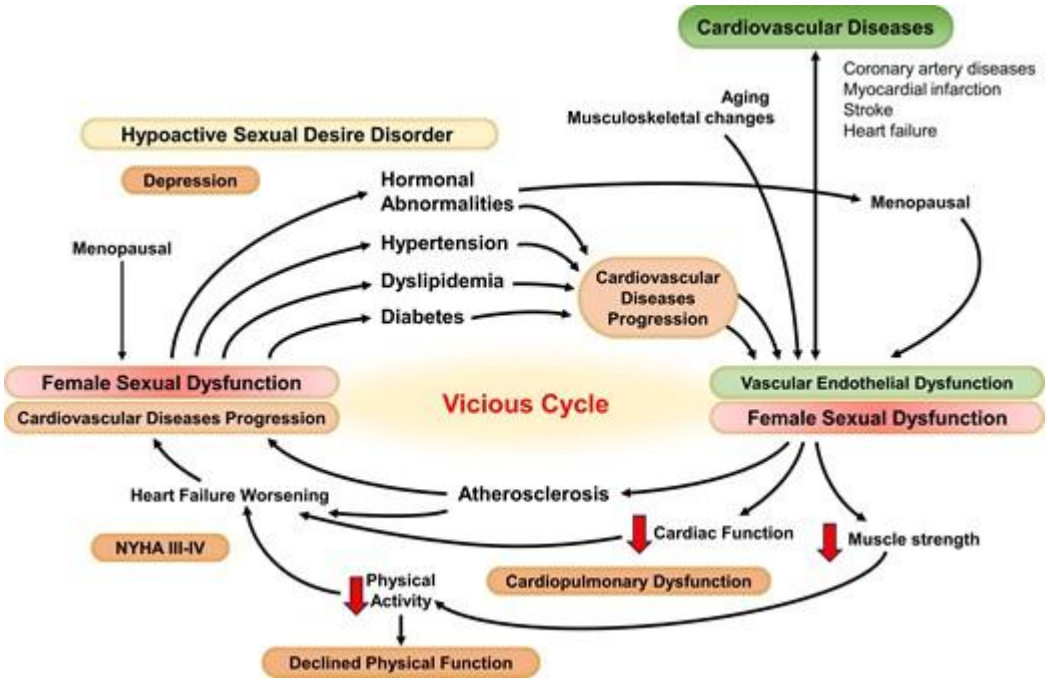
In the current issue of European Journal of Preventive Cardiology, Dilixiati et al.8 have reported a meta-analysis data, which indicated an increased risk of female sexual dysfunction (FSD) in patients with cardiovascular diseases. Longitudinal studies have confirmed significant associations between conditions such as hypertension, stroke, and myocardial infarction, and the incidence of FSD. The emergence of FSD can be attributed to a range of factors, including hormonal, neurological, vascular disorders, medication effects, psychological issues, and sociocultural influences.9 Physical conditions like diabetes, endometriosis, or multiple sclerosis can damage pelvic blood vessels or nerves, exacerbating FSD.8 Their meta-analysis showed a 1.51-fold increase in the risk of FSD among individuals with cardiovascular diseases compared to controls, updating our understanding of the relationship between hypertension and FSD and assessing the impact of coronary heart disease, coronary syndrome, heart failure, and other cardiovascular diseases on FSD.8 Female sexual dysfunction, while prevalent in the USA, is also a global issue, with culture-specific adaptations of the Female Sexual Function Index revealing similar or higher rates of sexual dysfunction among women in various regions worldwide.10–15

Management of FSD should prioritize hypoactive sexual desire disorder (HSDD) as a key component.16 Hypoactive sexual desire disorder can be caused by a combination of factors, including age-related hormonal decline, adverse life events, psychosocial issues, depression, medications, medical and gynaecological conditions, and disruptions in androgen production.16 Treating HSDD necessitates a comprehensive approach addressing situational, psychiatric, psychosocial, and chronic disease factors, as well as the use of oestrogens and androgens.16 However, the healthcare environment in many societies does not support FSD services, and cultural taboos

may hinder discussions of female sexual health.16 Given the significance of FSD as a cardiovascular risk factor, initiating conversations about sexual health is crucial.16 This issue should be incorporated into intervention programmes as a next step.

Patients with FSD are trapped in a vicious cycle that exacerbates cardiovascular disease progression (Figure 1). Initiating discussions on FSD in patients with cardiovascular conditions is imperative to break this cycle and enhance control over cardiovascular diseases.

Figure 1




Vicious cycle: female sexual dysfunction and cardiovascular diseases. Cardiovascular risk factors, including hypertension, dyslipidaemia, and diabetes, impair vascular endothelial function and exacerbate the progression of cardiovascular diseases, which, in turn, may induce female sexual dysfunction. This dysfunction can lead to reduced physical activity, further deteriorating cardiovascular health, including heart failure, and impairing female sexual function. Within this vicious cycle, numerous therapeutic targets emerge, such as hypertension, dyslipidaemia, diabetes, atherosclerosis, hormonal imbalances, cardiac rehabilitation, and depression. Nonetheless, the

critical step in breaking this cycle is the accurate diagnosis of female sexual dysfunction or hypoactive sexual desire disorder.

## 2. Association between cardiovascular disease and risk of female sexual dysfunction: a systematic review and meta-analysis

Aims

Female sexual dysfunction (FSD) is a considerably underestimated condition. It has been repeatedly reported that patients with cardiovascular diseases (CVD) may suffer from an increased risk of FSD. However, there is still a lack of comprehensive and systematic evaluation of various CVD and FSD. We aimed to elucidate the association between CVD and FSD through a comprehensive literature review and meta-analysis.

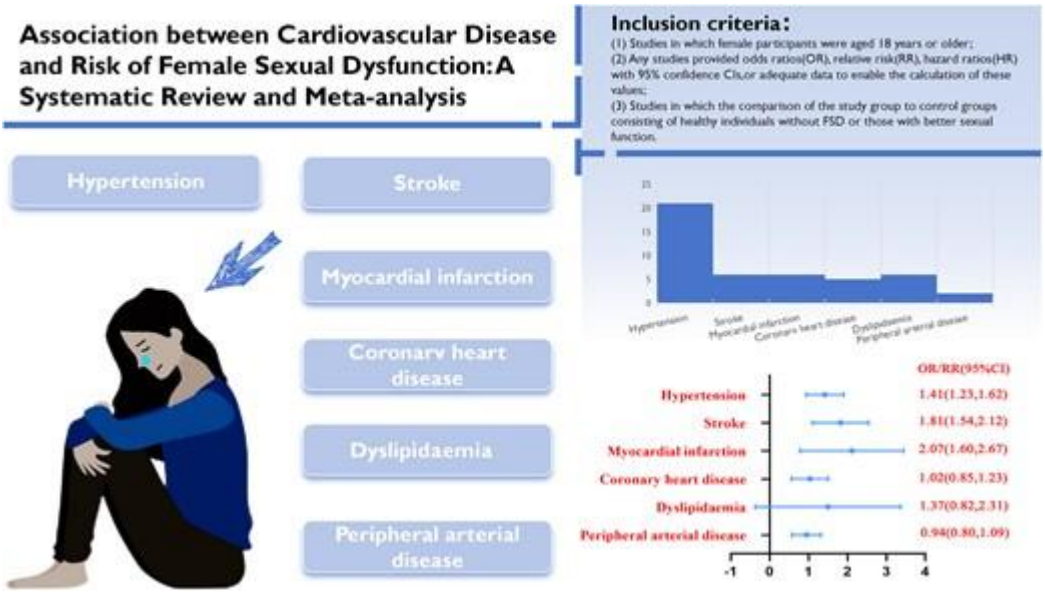
Methods and results

The PubMed, Scopus, Embase, and Cochrane Library databases were systematically searched from inception to 28 February 2023. We identified all relevant studies reporting the risk of FSD in subjects with or without CVD. The associations between CVD and the risk of FSD were assessed by calculating pooled odds ratios (ORs) (cross-sectional studies) and risk ratios (RRs) (longitudinal studies) with 95% CIs. We employed random-effects models to account for potential heterogeneity, and the quality of the included studies was assessed using the Newcastle–Ottawa Scale. Fifty-four articles with 148 946 individuals were included in our meta-analysis. Compared with control subjects, subjects with CVD had a 1.51-fold increased risk of FSD (OR 1.51 95% CI, 1.34–1.69, P < 0.001, heterogeneity I2 = 91.4%, P < 0.001). Subgroup analyses indicated that the association between CVD and FSD remained significant in longitudinal studies (RR 1.50 95% CI, 1.21–1.86, P < 0.001, heterogeneity I2 = 86.7%, P < 0.001). Particularly, hypertension (OR 1.41 95% CI, 1.23–1.62, P < 0.001, heterogeneity I2 = 82.7%, P < 0.001), stroke (OR 1.81 95% CI, 1.54–

2.12, P < 0.001, heterogeneity I2 = 0%, P < 0.423), and myocardial infarction (OR 2.07 95% CI, 1.60–2.67, P < 0.001 heterogeneity I2 = 82.4%, P < 0.001) were significantly associated with FSD. Meta-regression revealed that the primary sources of heterogeneity in FSD are attributable to adjustments for covariates, study design, and study population.

Conclusion

Our meta-analysis indicated that patients with CVD suffer from a greater risk of developing FSD. Meanwhile, we validated these findings in longitudinal queues. Notably, conditions such as hypertension, stroke, and myocardial infarction demonstrated a significant association with the incidence of FSD.




Lay Summary

Our study provides a significant advantage as the most comprehensive systematic analysis to date. It encompassed 45 cross-sectional and 11 longitudinal studies with 148 946 patients, aiming to investigate the relationship between various types of cardiovascular diseases (CVD) and female sexual dysfunction (FSD). Subgroup

analyses were conducted to explore the impact of factors such as region and publication time.

Accumulating evidence strongly supports a significant link between CVD and an increased risk of FSD, especially in cases of hypertension, stroke, and myocardial infarction. These findings indicate that more attention should be paid to women's sexual health, particularly in the presence of CVD.

Future studies are warranted to investigate the effects of pharmacological interventions on the sexual function of women affected by CVD.

**3. Time-Restricted Eating + High-Intensity Training Aids Women With Obesity, Inactivity**

Combining time-restricted eating (TRE) with high-intensity functional training (HIFT) may have superior effects on body composition, lipid profile, and glucose regulation among inactive women with obesity compared with diet or exercise interventions alone, according to a study published online May 1 in PLOS ONE.

Ranya Ameur, from University of Sfax in Tunisia, and colleagues examined the long-term effects of TRE, with or without HIFT, on body composition and cardiometabolic biomarkers in women with inactivity and obesity. The analysis included 64 participants randomly assigned to TRE (no more than an eight-hour daily eating window, with ad libitum energy intake), HIFT (three sessions/week), or TRE plus HIFT (TRE-HIFT) for 12 weeks.

The researchers found that TRE-HIFT showed a significantly greater decrease in waist and hip circumferences and fat mass versus TRE or HIFT. Additionally, weight and body mass index significantly decreased more in TRE-HIFT versus HIFT group. The TRE group had

lower fat-free mass versus both the HIFT and TRE-HIFT groups. The TRE-HIFT group showed decreases in total cholesterol, triglycerides, insulin, and homeostatic model assessment for insulin resistance versus both the TRE and HIFT groups. Furthermore, glucose level was significantly decreased in the TRE-HIFT group versus the HIFT group. In both the TRE-HIFT and HIFT groups, systolic blood pressure was decreased significantly when compared with the TRE group.

"In inactive women with obesity, combining TRE with HIFT can be a good strategy to induce superior effects on body composition, lipid profile, and glucose regulation compared with either diet or exercise intervention alone," the authors write.

**4. Effect of Bempedoic Acid on Cardiovascular Outcomes by Sex**

The cornerstone of prevention and treatment of atherosclerotic cardiovascular disease (ASCVD) has been HMG-CoA reductase inhibitors, statins; however, there are patients who are unwilling or unable to use statins due to intolerance. Women are more likely to report statin intolerance.1 Recently, the Cholesterol Lowering via Bempedoic Acid (CLEAR Outcomes) trial showed that patients with or at high risk for CVD who are unable or unwilling to take guideline-recommended doses of statins had a significantly lower risk of major adverse cardiovascular events (MACE) with bempedoic acid, an adenosine triphosphate citrate lyase inhibitor, than with placebo. Among modern day cholesterol trials, CLEAR Outcomes had the highest rates of women enrolled (48%) and offers a unique insight into the characteristics of women at high CVD risk.

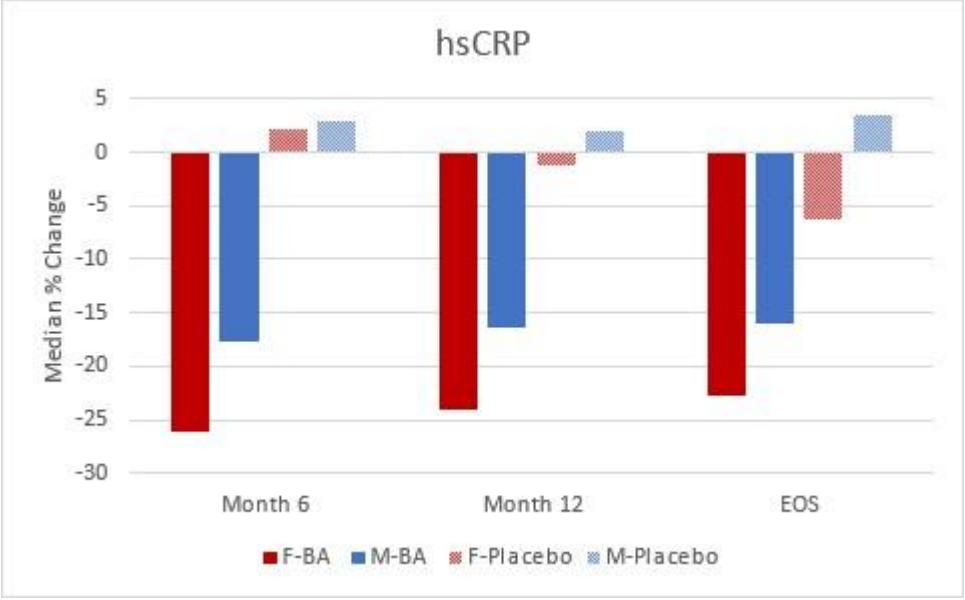
In brief, the CLEAR Outcomes trial2 enrolled 13,970 patients with or at high risk for CVD and high LDL-C levels, who were randomized to either 180 mg oral bempedoic acid daily or placebo and followed for a median period of 3.4 years. At baseline women had older age, diabetes, higher LDL-C and hs-CRP levels, and less use of lipid-lowering therapies. The proportion of patients who received primary versus

secondary prevention was higher in women. Women more likely had peripheral and cerebrovascular disease and less likely had coronary disease.

In both sexes, bempedoic acid reduced CVD risk, lowered LDL-C and hs-CRP levels, and was well-tolerated. Bempedoic acid reduced CVD risk similarly in women and men, particularly the risks of MACE-4 (CVD death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization; [aHR, 0.89; 95% CI, 0.75–1.04] and [aHR, 0.86; 95% CI, 0.77–0.97], respectively) and MACE-3 (CVD death, nonfatal myocardial infarction, and nonfatal stroke; [aHR, 0.88; 95% CI, 0.73–1.06] and [aHR, 0.84; 95% CI, 0.73–0.97], respectively).3

Treatment discontinuation rates were lower with bempedoic acid than placebo in women (30.5% vs 33.4%) and men (27.9% vs 30.0%). Similar rates of serious adverse events occurred in women (24.2%) and men (26.2%) treated with bempedoic acid.

Although there remains controversy regarding statin intolerance, alternative nonstatin lipid-modifying therapies are needed to manage patients and achieve guideline-recommended LDL-C level goals. Bempedoic acid should be considered as a viable option for those unwilling or unable to tolerate statins.



**5.Successful Pregnancy After Cardiac Arrest in a Woman With Severe Coronary Vasospasm**

We read with great interest the recently published paper by Ali Thara et al.[1] In this paper, the authors describe an unplanned pregnancy in a patient who experienced a recent cardiac arrest in the setting of severe left anterior descending artery vasospasm. Following her cardiac event, she was discharged home with potentially teratogenic cardiovascular medications, but without discussion of contraception or pregnancy planning. We commend the authors for bringing attention to this gap in care, as well as the discussion of options for termination.

We would like to highlight the discussion regarding pregnancy prevention brought to light in the case report as commented on in Question 3. According to the U.S. Medical Eligibility Criteria (USMEC) for contraception, prolonged systemic use of progestins could be characterized as category III (theoretical or proven risks usually outweigh the advantages of using the method) for *continued* use after an ischemic cardiovascular event.[2] The patient in this case did not have evidence of atherosclerosis, and ischemia was attributed to vasospasm, so the theoretical risk of systemic progestins is not likely directly applicable in this situation. However, even in the setting of atherosclerotic heart disease, levonorgestrel intrauterine devices (IUDs), which result in predominantly local rather than systemic effects, are considered category II (advantages of the method generally outweigh theoretical or proven risks) for initial use according to the USMEC.[2] Notably, recent studies have identified that progestin-only contraceptive methods do not carry significantly increased risk of venous or arterial thrombosis.[3] As such, the American College of Obstetricians and Gynecologists currently recommends progestin-only pills, the subdermal implant, or the hormonal IUD for patients with a history of or at risk for venous thromboembolism, myocardial infarction, or stroke.[4] Although a copper IUD would be also be a safe

option for these patients (USMEC category I), it may be associated with increased menorrhagia in the setting of dual antiplatelet therapy or systemic anticoagulation.

## 6.Cardiovascular Disease in Hispanic Women: *JACC* Review Topic of the Week

Cardiovascular disease affects 37% of Hispanic women and is the leading cause of death among Hispanic women in the United States. Hispanic women have a higher burden of cardiovascular risk factors, are disproportionally affected by social determinants of health, and face additional barriers related to immigration, such as discrimination, language proficiency, and acculturation. Despite this, Hispanic women show lower rates of cardiovascular disease and mortality compared with non-Hispanic White women. However, this "Hispanic paradox" is challenged by recent studies that account for the diversity in culture, race, genetic background, country of origin, and social determinants of health within Hispanic subpopulations. This review provides a comprehensive overview of the cardiovascular risk factors in Hispanic women, emphasizing the role of social determinants, and proposes a multipronged approach for equitable care.

Highlights

- Hispanic women face disproportionate cardiovascular risk, although there is considerable heterogeneity among subpopulations.
- Social determinants of health influence cardiovascular risk in Hispanic women.
- A multipronged approach is needed to address social determinants of health and achieve equitable care for Hispanic women.

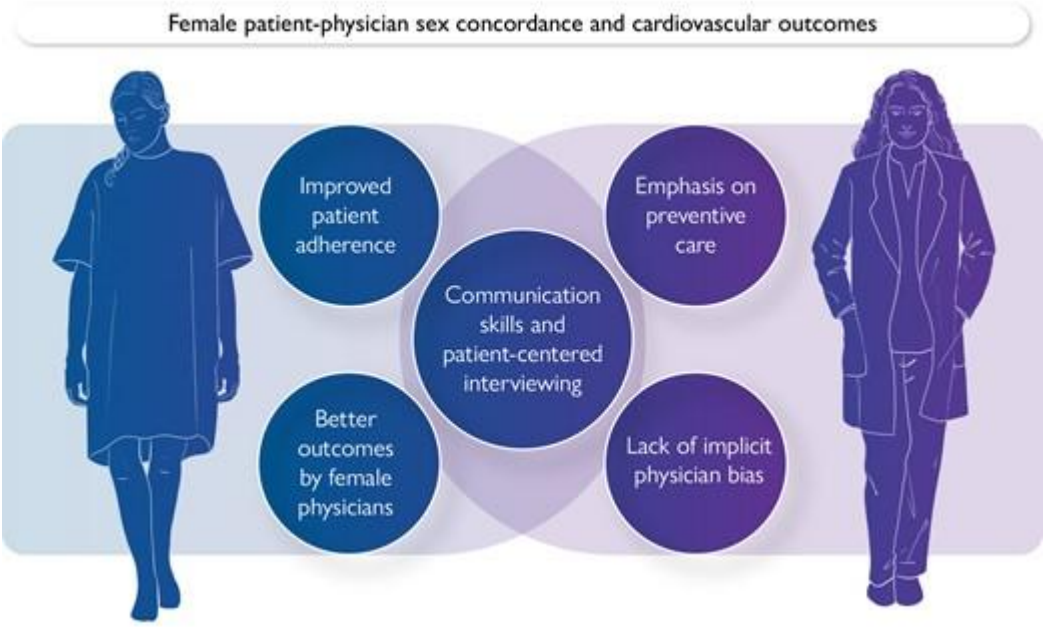
## 7. Patient–physician sex concordance and outcomes in cardiovascular disease: a systematic review

**Abstract**

The sex disparity in outcomes of patients with cardiovascular disease is well-described and has persisted across recent decades. While there

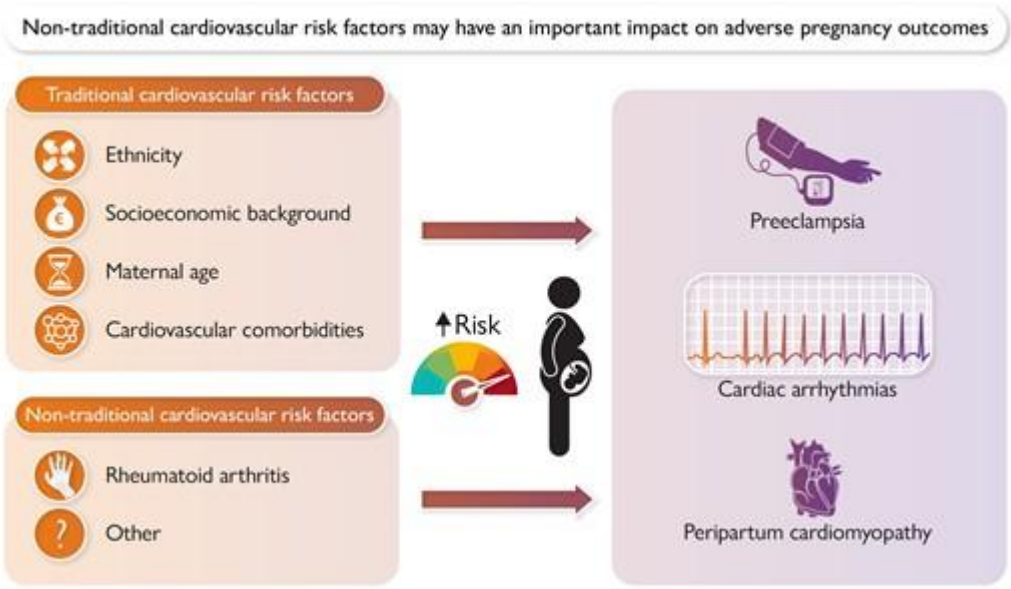
have been several proposed mechanisms to explain this disparity, there are limited data on female patient–physician sex concordance and its association with outcomes. The authors review the existing literature on the relationship between patient–physician sex concordance and clinical outcomes in patients with cardiovascular disease, the evidence of a benefit in clinical outcomes with female patient–physician sex concordance, and the possible drivers of such a benefit and highlight directions for future study.

**Graphical Abstract**




**8. Rheumatoid arthritis and peripartum cardiovascular complications: focusing on non-traditional cardiovascular risk factors to improve maternal outcomes**

**Graphical Abstract**




Non-traditional cardiovascular risk factors may have an important impact on adverse pregnancy outcomes. In identifying rheumatoid arthritis (RA) as an independent risk factor for maternal cardiovascular complications, Zahid et al. highlight the importance of gaining additional insight into the impact of non-traditional cardiovascular risk factors on pregnancy outcomes. Ongoing identification of novel clinical factors associated with maternal cardiovascular adverse outcomes could lead to improved pre-conception counselling. Expanded recognition of non-traditional maternal cardiovascular risk factors has the potential to be practice changing within the rapidly evolving field of cardio-obstetrics.

**9.Radiation protection for healthcare professionals working in catheterisation laboratories during pregnancy: a statement of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) in collaboration with the European Heart Rhythm Association (EHRA), the European Association of Cardiovascular Imaging (EACVI), the ESC Regulatory Affairs Committee and Women as One**

Abstract

The European Association of Percutaneous Cardiovascular Interventions (EAPCI), the European Heart Rhythm Association (EHRA), the European Association of Cardiovascular Imaging (EACVI), the European Society of Cardiology (ESC) Regulatory Affairs Committee and Women as One support continuous review and improvement, not only in the practice of assuring patients a high quality of care but also in providing health professionals with support documents to help them in their career and enhance gender equity. Recent surveys have revealed that radiation exposure is commonly reported as the primary barrier for women pursuing a career in interventional cardiology or cardiac electrophysiology (EP). The fear of foetal exposure to radiation during pregnancy may lead to a prolonged interruption in their career. Accordingly, this joint statement aims to provide a clear statement on radiation risk and the existing data on the experience of radiation-exposed cardiologists who continue to work in catheterisation laboratories (cath labs) throughout their pregnancies. In order to reduce the barrier preventing women from accessing these careers, increased knowledge in the community is warranted. Finally, by going beyond simple observations and review of the literature, our document suggests proposals for improving workplace safety and for encouraging equity.

## Introduction

Why is a collaborative statement on radiation exposure during pregnancy required? Interventional cardiology and electrophysiology are the two subspecialities with the lowest female representation in cardiology1234. Radiation exposure is commonly identified as a major barrier for women considering a career in interventional cardiology and electrophysiology45, and concerns regarding occupational radiation exposure during pregnancy are likely to lead to missed career development opportunities6. Amongst European Union countries, there are substantial variations in occupational radiation regulations and practices, despite the recent definition of safe dose

limits and safety standards for foetal exposure from the European Directive, as well as the repeal of previous Euratom directives7. The 2011 Society for Cardiovascular Angiography and Interventions (SCAI) and 2017 European Heart Rhythm Association consensus documents and 2018 European Association of Percutaneous Cardiovascular Interventions (EAPCI) survey report289 endorse the safe continuation of work with occupational radiation exposure while pregnant; yet, in some EU countries, pregnant women are not permitted to work in the cardiac catheterisation laboratory, while in other EU countries, policies are more permissive10 (Table 1). Nevertheless, there remains a lack of precise data on the real risks to the foetus and awareness of the existing directives, not only amongst heads of departments but also amongst women working as physicians in interventional cardiology11. Therefore, while European, North American, Japanese, and Australian directives allow women to work if closely monitored with an abdominal dosimeter to ensure that the foetus does not exceed recommended dose limits during pregnancy, in some countries, pregnant women are not allowed to work. There is also a disparity regarding the maximum foetal dose allowed across countries: 1 mSv in Europe7, Australia12 and Israel, 2 mSv in Japan and 5 mSv in the US13 (Table 1). This lack of knowledge that persists among the interventional and electrophysiology communities contributes to workforce gender disparity. In order to reduce barriers preventing women from accessing a career in interventional cardiology, there should be clear statements on radiation risk and data collection on the current experiences of radiation-exposed cardiologists who continue to work in catheterisation laboratories throughout their pregnancies. The aim of the present document is to provide data and clear information on radiation risk in order to overcome the “radiation barrier”.

Table 1. Current legal requirements: EU, UK, USA, Australia, Israel. Overview of the current EU regulations and their local application demonstrating a general trend in more restrictive applicative directives

usually limiting access to the catheterisation/electrophysiology lab and allowing a discretional power to the X-ray surveillance experts. Overview of the current non-EU regulation with focus on the UK, USA, Australia and Israel.

| | The European Directive 2013/59/Euratom, Art.10 has been adopted in your Country. YES/NO | COUNTRY LAW | Exposure during pregnancy (cumulative dose over the pregnancy) | Exposure during breastfeeding | In-hospital discretionary allowance |
|---|---|---|---|---|---|
| AUSTRIA | YES | YES | Not allowed | Not allowed | NA |
| BELGIUM | YES | ARBIS 20-07-2001 | Yes, should be <1 mSv and ALARA | Yes, allowed | Risk analysis of occupational exposure for every pregnant woman with arbitrary allowance according to the X-ray surveillance expert. |
| CYPRUS | YES | 2018 | Yes, should be <1 mSv | Yes, allowed | NA |
| DENMARK | YES | BEK nr 669 af 01/07/2019 (equivalent to EU directive) | Yes, should be <1 mSv after pregnancy is recognised – special dosimetry is encouraged (day-to-day monitoring) | Ok, but exposure should be limited | NA |
| FRANCE | YES | Articles D. 4152-5 and R. 4451-45 of French Labour Code | Yes, should be <1 mSv | No specific indications | Possibility of shifting the pregnant woman to an occupation with less radiation exposure or keeping her in her current assignment if the total expected radiation dose between pregnancy |

| | The European Directive 2013/59/Euratom, Art.10 has been adopted in your Country. YES/NO | COUNTRY LAW | Exposure during pregnancy (cumulative dose over the pregnancy) | Exposure during breastfeeding | In-hospital discretionary allowance |
|---|---|---|---|---|---|
| | | | | | confirmation and childbirth is <1 mSv |
| GERMANY | YES | Strahlenschutzgesetz (StrlSchG): German Radiation Protection Law dated June 27, 2017 (Federal Law Gazette Part I, p. 1,966), last amended by Article 2 of the law of May 20, 2021 (Federal Law Gazette Part I p. 1,194): §78Strahlenschutzverordnung (StrlSchV): German Radiation Protection Ordinance dated November 29, 2018 (Federal Law Gazette Part I, p. 2,034-2,036), last amended by Article 6 of the law of May 20, 2021 (Federal Law Gazette Part I p. 1,194): §55 | Yes, should be <1 mSv, weekly monitoring | Yes, allowed | Risk analysis of occupational exposure for every pregnant woman with arbitrary allowance according to the X-ray surveillance expert. |
| HUNGARY | YES, in a restricted manner (no exposure when pregnant/breastfeeding) | Government Decree 487/2015 (XII. 30.) on the protection against ionising radiation and the corresponding licensing, reporting (notification) and inspection system | Not allowed | Not allowed | The pregnant woman shall have her work reorganised to avoid any risk (including infections, radiation, etc.).The pregnant woman cannot be dismissed/suspended because of her status. |
| IRELAND | YES | RADIOLOGICAL PROTECTION ACT 1991 (IONISING RADIATION) REGULATIONS 2019 | Yes, should be <1 mSv | Yes, allowed | NA |

| | The European Directive 2013/59/Euratom, Art.10 has been adopted in your Country. YES/NO | COUNTRY LAW | Exposure during pregnancy (cumulative dose over the pregnancy) | Exposure during breastfeeding | In-hospital discretionary allowance |
|---|---|---|---|---|---|
| ITALY | YES, in a restricted manner (no exposure when pregnant/breastfeeding) | DL 101 July 2020 | Not allowed | Not allowed | Not allowed |
| NETHERLANDS | YES | | Yes, should be <1 mSv | Yes, allowed | Risk analysis of occupational exposure for every pregnant woman with arbitrary allowance according to the X-ray surveillance expert |
| PORTUGAL | YES (108/2018, article 69) 102/2009 | 102/2009, 10 September | Not allowed | Not allowed | Not allowed |
| ROMANIA | YES | LAW 154/2015 | Not allowed | Not allowed | The employer must change the working conditions, so that there is no radiation exposure |
| SLOVENIA | | ZVISJV-1, December 2017 | Yes, should be <1 mSv, monthly monitoring | Yes, allowed | Institution is obliged to organise a different workplace or reorganise working time under exposure so the goal <1 mSv can be met |
| SPAIN | YES, current laws, although enacted before this directive was issued, are in accordance with it | Royal Decree 298/2009, of 6th March, which modifies the Royal Decree 39/1997, of 17th January | Yes, should be <1 mSv, monthly monitoring | Yes, allowed. During the breastfeeding period the worker will not be | Even though current law allows women to work provided the dose is <1 mSv for the whole pregnancy, in some cases, the |

| | The European Directive 2013/59/Euratom, Art.10 has been adopted in your Country. YES/NO | COUNTRY LAW | Exposure during pregnancy (cumulative dose over the pregnancy) | Exposure during breastfeeding | In-hospital discretionary allowance |
|---|---|---|---|---|---|
| | | | | employed in a job with radionuclides and contaminants | the X-ray surveillance department or the occupational risk department do not allow a woman to work |
| SWEDEN | YES | SFS 2018:396 | Yes, should be <1 mSv | Yes, allowed | How a foetal dose below 1 mSv is ensured is up to the authority, i.e., the public healthcare provider. There may be different ways of calculating the foetal dose between hospitals. Currently a factor of 5 is used. |
| NON-EU | | | | | |
| AUSTRALIA | NO, the current Australian codes and standards are based on the 2020 guidelines of the International Commission on Ionising Radiation Protection (ICNIRP) | Australian Radiation Protection and Nuclear Safety Agency Radiation Protection Diagnostic and Interventional Cardiology, series 14.1. Australian Radiation Health Committee. 2008 | Yes, dose to foetus should be <1 mSv from declaration of pregnancy to delivery | Yes, allowed (no threshold specified) | NA |
| ISRAEL | NO | 1992 Law by the Ministry of Labor, Social Affairs and Social Services | Yes, dose should be <1 mSv/9 months | Yes, allowed. No limitations | At 4 months pregnancy – medical examination by occupational medicine |
| UK | YES | The Ionising Radiation Regulations 2017 (IRR 17) | 1 mSv limit | None for radiation(only radionuclid | 1 mSv limit |

| | | | | | |
|---|---|---|---|---|---|
| | The European Directive 2013/59/Euratom, Art.10 has been adopted in your Country. YES/NO | COUNTRY LAW | Exposure during pregnancy (cumulative dose over the pregnancy) | Exposure during breastfeeding | In-hospital discretionary allowance |
| | | | | es and contaminants) | |
| USA | Pregnancy Discrimination Act and the American Disabilities Act: pregnant workers have a legal right to work adjustments that allow them to do their job without jeopardising their health | Individual states have Pregnant Workers Fairness laws | No legal specifications regarding exposure.NCRP recommends a dose <5 mSv/9 months | No legal specifications regarding exposure | Yes |
| ALARA: as low as reasonably achievable; NA: not applicable; NCRP: National Council on Radiation Protection and Measurements | | | | | |

Risks: biological evidence of radiation exposure during pregnancy

Ionising radiation exposure during pregnancy and the potential impact of prenatal radiation is a major concern for women in the cardiac catheterisation laboratory1415.

Prenatal radiation risks include pregnancy loss, congenital malformations, developmental delay, and carcinogenesis. Some risks are dependent on the radiation dose. These hazards can be stochastic, including the risk of childhood cancer and genetic disorders1617, or deterministic, which have a radiation dose threshold, such as intrauterine growth retardation, miscarriage, and congenital defects17. The greatest risk of pregnancy loss from radiation exposure is during the first 2 weeks of pregnancy, while between 2-8 weeks after conception, the embryo is most susceptible to the development of congenital malformations because this is the period of organogenesis18.

The foetal radiation doses that have been related to the occurrence of abortion, malformations or intelligence quotient reductions are 100

times higher than those allowed during the entire pregnancy for an interventional cardiologist. Since the threshold dose for these deterministic effects is well above that which an invasive or interventional cardiologist would receive under a protective apron, the use of standard radiation protection techniques would result in negligible risk to the foetus. With respect to stochastic effects, which have no threshold dose, the embryo/foetus is assumed to be at about the same risk for potential carcinogenic effects of radiation as children throughout most of the pregnancy13. Table 3 shows the spontaneous probability of a newborn having a congenital malformation or childhood cancer and how this probability has a negligible increase when the occupational exposure range of the mother respects the 1, 2 or 5 mSv limits during pregnancy919.

However, understanding the mechanisms that underlie the pathogenesis of radiation-induced birth defects is difficult since possible radiation damages are linked to a multifactorial process which has not been well researched. There are no randomised trials assessing the risks of prenatal radiation. The most conclusive studies have been on massive radiation exposure such as after the atomic bombs used in World War II. There have also been estimates made from population studies of prenatal radiation exposure. The probability that a child will be born with a congenital abnormality or cancer increases from 4.07% with background radiation to 4.078% with 1 mSv conceptus exposure and to 4.12% with 5 mSv exposure20. There are no studies that show an increased risk of non-cancerous effects from prenatal radiation exposure below 50 mSv21. Occupational radiation exposure during pregnancy is regulated in Europe by directives from both the EU and each country, and in the USA by federal and state law, which take into account the recommendations from the International Commission on Radiological Protection (ICRP)13. The current National Council on Radiation Protection and Measurements (NCRP) recommends a monthly maximal exposure of <0.5 mSv, and the ICRP recommends a dose <1

mSv for the entire pregnancy. The limit of safe foetal radiation exposure of 1 mSv throughout pregnancy for the EU member states is based on the Directive 96/29/Euratom, which establishes that the protection of the foetus shall be comparable to that provided for members of the public, and thus it should not receive more than 1 mSv/year9. However, in the USA, regulation is less restrictive, and the NCRP in Report No. 174 recommends limiting occupational exposure of the foetus to not exceed 5 mSv throughout the entire pregnancy and 0.5 mSv per month of the pregnancy. This is because, in the USA, American employers are required to treat their female employees equally with respect to "pregnancy, childbirth or related medical conditions". Therefore, the radioprotection policies for pregnant workers in the USA prioritise the pregnant worker's rights from an anti-discriminatory perspective, while the European legislation policies prioritise mostly the safety rights of the unborn child9. In any case, the general instructions of the European directives continue stating that, once the woman has declared pregnancy, the employer must ensure that the equivalent dose limit for a foetus remains ≤1 mSv. Thus, while pregnancy does not require removing the exposed professional from work, a careful review of working conditions in order to comply with current regulations is warranted. However, nowadays there are still countries in the EU which prevent pregnant staff from working in the cath lab. Thus, we encourage the national interventional and electrophysiology (EP) societies of those countries to work together with their national health system authorities to promote changes in regulation and to repeal sexist laws that disincentive women to choose interventional subspecialities and expose the foetus to unnecessary risks by promoting late pregnancy declaration.

The amount of radiation exposure to the conceptus is measured by wearing a radiation badge under a lead apron at waist level. This amount should be assessed in all professionals who work in an environment with ionising radiation exposure, but all the more so

when those professionals include pregnant women. Furthermore, operators can use the same technique to measure radiation exposure prior to pregnancy in order to estimate the likely occupational risk during pregnancy. Since the first trimester is when the conceptus is at highest risk to radiation exposure and since most women may not know they are pregnant during this time, it is important to practise universal radiation safety at all times.

Although the foetal radiation doses that have been related to the occurrence of malformations/childhood cancer are much higher than those allowed for the entire pregnancy for an interventional cardiologist10, little information is available in the literature on the dose received by pregnant employees exposed to ionising radiation. In order for interventional and EP cardiologists to make informed decisions, we encourage national interventional and EP societies to collect and publish data regarding radiation exposure and pregnancy outcomes in pregnant cardiologists working in the cath/EP labs.

Finally, the impact of radiation exposure on men should also be considered. In fact, chronic occupational radiation exposure among male workers is correlated with a higher prevalence of low birth weight in offspring and instability in the Y chromosome azoospermia factor c (AZFc) region, responsible for male infertility22.

Table 2. Main deterministic/stochastic irradiation effects on the embryo/foetus at each pregnancy stage (Adapted from9).

| Pregnancy stage | Main irradiation effect | Doses at which effects have been described | Risk at occupational dose (range ≤1-5 mSv exposure to the mother) | Spontaneous risk24 |
|---|---|---|---|---|
| Preconception gonadal irradiation | Has not been shown to result in increased cancer or malformations in children13 | | | |

| Pregnancy stage | Main irradiation effect | Doses at which effects have been described | Risk at occupational dose (range ≤1-5 mSv exposure to the mother) | Spontaneous risk24 |
|---|---|---|---|---|
| Preimplantation(First two weeks post-conception) | Abortion | Doses over 100 mGy25 | Death of the conceptus due to radiation is not described28 | Risk of spontaneous abortion in known pregnant women 1/7 |
| Period of major organogenesis(weeks 3-8 post-conception) | Risk of malformation or growth retardation | Dose threshold of around 100 mGy26 | Not expected below 100 mGy26 | Risk of major congenital malformations 1/33Risk of growth retardation 1/33 |
| Early foetal period (weeks 8-25 post-conception) | Risk of reducing the intelligence quotient | Dose threshold of around 120-200 mGy weeks 8-15Dose threshold of around 500 mGy weeks 16-25 | Doses under 100 mGy and in the mother's occupational exposure range (<5 mSv) would be of no practical significance26 | |
| Third trimester | Risk of malformation, growth retardation or reduced intelligence quotient not expectedPossible fatal or non-fatal cancer of any type (solid | Lifetime cancer risk following in utero exposure will be similar to that following radiation in early childhood | Lifetime cancer risk around 1/500 for 5 mSv in utero exposure2728, and 1/2,500 for 1 mSv in utero exposure2728 | Risk of childhood leukaemia per year 1/25,000/year |

| Pregnancy stage | Main irradiation effect | Doses at which effects have been described | Risk at occupational dose (range ≤1-5 mSv exposure to the mother) | Spontaneous risk24 |
|---|---|---|---|---|
| | tumours and leukaemia) | | | |

Table 3. Probability of a child to be born with a congenital malformation or to develop childhood cancer spontaneously and after ionising radiation exposure (summarised from20).

| Foetal dose added to the background radiation (mSv) | Probability of a child having a congenital malformation (%)2930 | Probability of a child developing childhood cancer (%)2931 | Probability of a child having a congenital malformation or childhood cancer (%)32 |
|---|---|---|---|
| 0 (spontaneous risk) | 4.000 | 0.070 | 4.070 |
| 0.5 | 4.001 | 0.074 | 4.072 |
| 1 | 4.002 | 0.079 | 4.078 |
| 2.5 | 4.005 | 0.092 | 4.090 |
| 5 | 4.010 | 0.110 | 4.120 |
| 10 | 4.020 | 0.160 | 4.170 |

Proposal for better practice

Operators using fluoroscopy must be guided by the “as low as reasonably achievable” (ALARA) principle, in which the obtention of optimal images must be balanced with prodecure safety. The practice of radiation safety is grounded in an understanding of external radiation protection measures as well as technical considerations in operating the X-ray system. Minimising a pregnant operator’s radiation exposure follows similar principles to general working practices in a radiation environment. Scatter radiation emitted from the patient is the greatest source of radiation exposure to the operator and personnel. Therefore, methods to reduce radiation exposure to the patient will automatically reduce operator and personnel exposure.

Furthermore, appropriate standardised operating procedures must be in place to prevent unintentional exposure.

The three fundamentals of radiation safety to an operator include 1) time, 2) distance and 3) shielding and dosimeter monitoring. Time refers to the amount of time the operator spends using the X-ray system, where less usage equals less radiation exposure23. Operators must maximise their distance from the X-ray source as radiation intensity follows the inverse square law: if the operator's distance from the X-ray source increases from 40 cm to 80 cm, radiation intensity reduces by a factor of 4. Shielding is used in the form of personal, tableside or external protection with each form having a degree of lead equivalence defining its radiation protective effect. Personal shielding includes a lead apron with or without shoulder covers for breast shielding, a thyroid collar and lead glasses. The lead apron should be of at least 0.35 mm thickness, attenuating approximately 95-96% of the scatter radiation. The use of 0.5 mm thickness attenuates 98.0-99.5% of the scatter radiation dose. An overhead movable lead shield of 1 mm thickness positioned close to the patient and between the operator and the entry of the X-ray source can reduce radiation exposure by 95%. Available data show that the majority of foetal radiation dose exposure rarely exceeds 0.3 mSv (Table 4, Table 5). The key principles of radiation safety for pregnant staff are summarised in the Central illustration.

Table 4. Current published and unpublished data from practice or indirect studies.

| Author | Settings | Attitude during pregnancy and dose received | Outcome |
|---|---|---|---|
| Spain(Velázquez et al, 201710) | Interventional cardiologists and electrophysiologists (n=5) | Background radiation in 80% of all pregnancies, 0.2 mSv in one pregnancy | 4 normal pregnancy outcomes, 1 pregnancy with placental insufficiency |
| New Zealand* | Multiple trainees and | Unpublished accounts of | Normal |

| Author | Settings | Attitude during pregnancy and dose received | Outcome |
|---|---|---|---|
| (Unpublished anecdotal accounts only) | interventional cardiologists in New Zealand | case-by-case and monthly foetal monitoring with radiation dose well below safe pregnancy thresholds* | pregnancy outcomes reported |
| Australia* (unpublished anecdotal accounts only)(*Burgess S; on behalf of Women in Interventional Cardiology of Australia and New Zealand (WIICAN). Unpublished data on pregancy in Female Interventional Cardiologists of Australia and New Zealand 2021) | Multiple trainees and interventional cardiologists in Australia(n=11) | Unpublished accounts of case-by-case and monthly foetal monitoring with radiation dose well below safe pregnancy thresholdsIn detail: Of 19 female interventional cardiologists (IC) in Australia and New Zealand2, 13/19 (68%) known to the author* were directly contacted by phone or email, 11/13 responded (85%). Amongst responders 11/11 (100%) had at least one pregnancy during advanced training, fellowship or consultancy. A total of 21 pregnancies were included. Amongst responders, during 86% of all pregnancies, doctors, including 82% of IC, remained in the cath lab with appropriate shielding and without any adjustment of schedule or cath lab exclusion. Of the remaining 2 IC, one doctor was excluded from weeks 8-15 in 1 of 2 pregnancies | Pregnancy outcomes consistent with those of the general population were reported |

| Author | Settings | Attitude during pregnancy and dose received | Outcome |
|---|---|---|---|
| | | but remained in the lab without exclusion for her other pregnancy, and the remaining doctor chose to self-exclude from the catheterisation laboratory from approximately 6-9 weeks.All 11/11 responders (100%) reported dose monitoring at the time of their pregnancies with radiation doses well below thresholds for safe pregnancy as defined by Australian and New Zealand policy and standards. | |
| USA(Marx MV et al 199233) | Prospective study (n=30) of interventional radiologists and trainees (not pregnant, male and female) | The calculated average dose to pregnant interventional radiologists (in 1992) over a 40-week pregnancy with two layers of lead=0.4 mSv dose calculated to be 1.3 mSv with one layer of lead (NCRP occupational foetal dose limit=5 mSv) | |
| France(Vautrin et al34) | Questionnaire among the female population in interventional cardiology in France (n=14) | 14/26 women had children. Half of them continued to work during the first trimester of pregnancy, and 2 continued until 7 months. Four wore an additional lead apron for double lead protection of the abdomen. | Outcomes not reported |

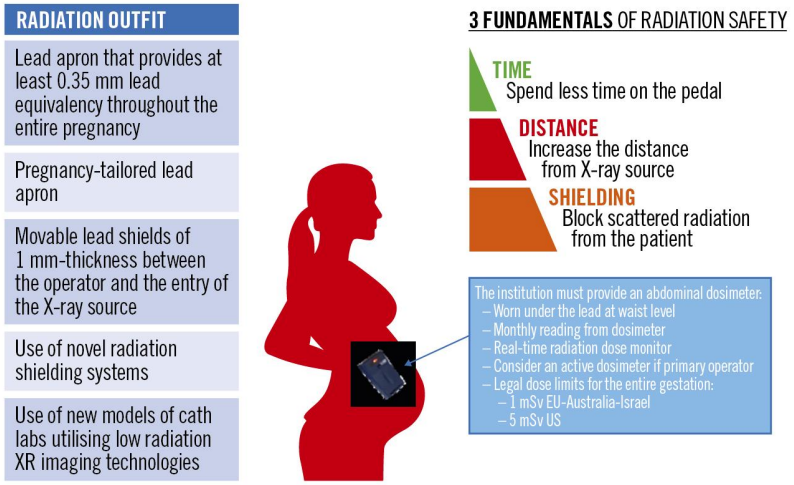
| Author | Settings | Attitude during pregnancy and dose received | Outcome |
|---|---|---|---|
| | | Dose received was not asked in the questionnaire. | |
| USA(Sarma AA et al6) | Survey of the women in cardiology section of the American College of Cardiology (n=501 women) | 47% of women tried to avoid pregnancy during periods when they would be exposed to radiation and 57% of women experienced radiation during a pregnancy, without a difference between trainees (49%) vs attending physicians (58%; p=0.28). Those under 50 at the time of the survey were actually more likely to have avoided pregnancy during periods of radiation exposure as compared with those >50 (50% vs 39%; p=0.03), suggesting that younger cardiologists are more concerned about radiation.Women were relatively uninformed about whether their department had an official policy regarding radiation exposure during pregnancy: 34% saying they didn't know if their department had a policy, 32% reporting that their department did not, and 34% reporting that their department did (no | Outcomes not reported |

| Author | Settings | Attitude during pregnancy and dose received | Outcome |
|---|---|---|---|
| | | difference between women >50 years of age and women <50 years of age, potentially limiting senior cardiologists from providing mentorship on this issue to younger colleagues).Among women who experienced pregnancy radiation exposure, only 20% used foetal radiation badges, 24% used additional lead, and 42% increased their distance from radiation sources. Thus, despite a high rate of concern, pregnant cardiologists underuse radiation reduction and monitoring strategies.Dose received during pregnancies was not asked in the survey. | |
| *Published and unpublished data from interventional cardiologists that continued to work in the cardiac catheterisation laboratories during their pregnancies. While numerous interventional cardiologists from Europe, North America, Australia and New Zealand report safely working and training throughout pregnancy without interruption using various radiation monitoring techniques, little published data exist. | | | |

Table 5. Unpublished data from practice.

| Country | Pregnancies with radiation exposure, standard shift | Means of reducing foetal radiation exposure | Equivalent dose received during pregnancy | Outcome |
|---|---|---|---|---|
| Spain | 15 pregnancies/11 | Standard 1 | Background | 14 pregnancies: |

| | | | | |
|---|---|---|---|---|
| | interventional cardiologists | vest+1 skirt 7/15Extra skirt or gonadal protection shield 8/15 | radiation 8/150.2 mSv 2/15<1 mSv 3/15Don't recall 2/15 | normal outcome1 pregnancy: placental insufficiency |
| France | 8 pregnancies/5 interventional cardiologists | Standard 1 vest+1 skirt 5/8Extra removable on-wheels shield protection 3/8 | 7/8 pregnancies: background radiation0.23 mSv in one pregnancy | Normal pregnancy outcomes reported for all pregnancies |




Central illustration. Managing the radiation safety of pregnant staff. (adapted from Women as One https://rad.womenasone.org)

Proposal for encouraging equity

The root causes of gender disparity in cardiology are numerous but related mainly to societal and cultural norms concerning the role of women. This is most apparent regarding parenting and family planning for women during training and early career, especially in invasive subspecialities. As medicine witnesses a cultural shift that overlaps with the changing societal biases towards gender, paradigm changes in practices must occur to increase female representation and narrow gender inequalities among trainees and faculty in invasive cardiology subspecialities.

The first change should target medical schools' curricula, introducing medical students to clinical cardiology and supporting students

interested in invasive cardiology subspecialities regardless of race or sex. Commonly heard fallacies must be clarified, particularly the ones related to the impact of radiation on women's fertility and conception. Institutions should improve radiation counselling to address employees' concerns adequately and train them in safe practices that minimise radiation exposure. Concurrently, efforts must be made to convert the workplace into a friendlier environment for families, especially pregnant interventionists. For instance, lighter protective garments must be introduced to avoid additional physical burdens on pregnant women and ensure that these protection suits are adjustable as the foetus grows. Emerging technologies to minimise radiation exposure in male and female operators (i.e., tailored shielding, lead offloading, robotics, 3-dimensional mapping systems in invasive electrophysiology, etc.) should be introduced in contemporary catheterisation laboratories. Furthermore, coverage for women who become parents during training should be implemented proactively, and standardised, so that the burden of guilt for the pregnant interventionalist is lifted and so that this becomes routine practice rather than an inconvenience to the rest of the trainees. These measures can include increased pay for those covering, as well as curricular advances to ensure that training for these women is not prolonged.

Providing active dosimeters to help reduce exposure would be an important step and would protect not only pregnant women but all operators.

Indeed, gender equity should be a common interest for both men and women. Male role models and mentors need to show support based on talent and accomplishments irrespective of gender. The Pygmalion effect, where prejudiced expectations impact outcomes, needs to be of less influence when recruiting or collaborating with female colleagues. Highly qualified female interventionists should be assumed to be as equally apt as their male counterparts in performing the job and should be offered similar opportunities with equal pay. There must be

a joint effort to revoke gender as a criterion for promotion or leadership. The only way to achieve equity is through a collaborative leadership that ensures equality between men and women at all career and life stages.

Conclusions

Fear of foetal exposure to ionising radiation during pregnancy remains a barrier for women who wish to pursue a career in interventional cardiology. International expert commission recommendations and European directives clearly state that pregnant women can continue to work in an ionising radiation environment providing that the foetus does not exceed certain dose thresholds. Moreover, data from practice, although scarce, confirm radiation doses to be well below these limits. Despite this, many countries apply inappropriately restrictive directives. Specific institutional radiation protection programs should be established to help to overcome radiation barriers by including specific safety requirements for everyone; this would also ensure safe exposure during pregnancy. Key opinion makers in cardiovascular societies and ancillary institutions should promote awareness at both the local and national level to ensure a level playing field and a friendly environment for pregnant interventionists. This would help to facilitate the continuation of interventional work during pregnancy and go towards eliminating this cause of gender inequity in invasive cardiology subspecialities.

**9.Women, Black Patients Less Likely to Get Advanced PE Therapy, Analysis Shows**

Advanced therapies for pulmonary embolism (PE) have been hailed as game changers for patients, but even as more devices are entering or preparing to enter the market, an analysis of real-world data suggests there may be race- and gender-based disparities in who gets access to treatment .

“Advanced PE therapy seems to be vulnerable to disparate use and perhaps underused in aggregate,” said Sahil Parikh, MD (NewYork-Presbyterian/Columbia University Irving Medical Center, New York, NY), who presented the new analysis here at SCAI 2024. “Advanced therapies for PE were performed less often in Black patients, and when advanced therapies were used, the odds of major bleeding was interestingly higher in women and white patients versus Black patients.”

PE interventions are among the fastest growing procedural areas in interventional cardiology, despite the absence of class I, level I evidence for procedural performance and no mandated registries or designated centers of excellence, he added.

The new exploratory analysis, part of the REAL-PE study, used deidentified electronic health records from the Truveta database that included more than 435,000 patients in the United States with a diagnosis of PE between 2018 and 2023. Of those, 2,072 (0.48%) received ultrasound-assisted catheter-directed thrombolysis (EKOS, Boston Scientific) or mechanical thrombectomy (FlowTriever, Inari Medical).

Among the patients who received advanced therapies, 60% were age 60 or older. Men outnumbered women at 53.7% versus 45.7%, and the majority were white, with Black patients accounting for 13%, Asian patients accounting for 0.8%, and American Indian or Alaska Native patients representing just 0.6% of the treated population. In terms of ethnicity, Hispanic or Latino patients made up 5.8% of the total.

Advanced-therapy rates were lower for Black versus non-Black patients (0.37% vs 0.50%) and for women vs men (0.41% vs 0.55%; $P < 0.0001$ for both). Additionally, in individual comparisons with white men and white women, Black men and Black women were less likely to receive the therapies ($P = 0.0002$ for both).

“We need to do further assessment to better understand why these [disparities] exist,” Parikh said in a press conference prior to his presentation.

To TCTMD, he said the 0.48% treatment rate is particularly striking given that advanced therapies are chosen in about one in five high-risk PE cases. Conservatively, if 25% of the overall cases analyzed were high risk, the number selected for treatment should have been more than double what the analysis found.

Advanced PE therapy seems to be vulnerable to disparate use and perhaps underused in aggregate.Sahil Parikh

“One thing that strikes me about PE [therapies] is that the utilization must be very different from center to center,” noted panelist Ethan C. Korngold, MD (Providence St. Vincent Medical Center, Portland, OR). As advanced PE therapy continues to proliferate, he said it will be important that centers that offer those therapies “can reach a variety of different patients in a range of backgrounds.”

At the same time, panelist William Brent Keeling, MD (Emory University, Atlanta, GA), said while big data, such as was used in this analysis, may point the way toward demographic problems in access to treatments, “the first test is to figure out who actually benefits from these interventions.”

A ‘Renaissance’ of PE Innovation

Presentations on PE management were widespread at the SCAI meeting, with a recurring theme of who to treat and how, given the explosion of new options. Presenting in the same session, Tai Kobayashi, MD (Hospital of the University of Pennsylvania, Philadelphia), showed early data on a novel PE thrombectomy device (Hēlo; Endovascular Engineering), which features a host of functions from spinning to aspiration and was built to mirror a bronchoscope. He called it a “marriage” between large- and small-bore embolectomy.

“We know that the pulmonary arteries match the anatomy of the bronchus,” Kobayashi told TCTMD. “It is similarly over the wire in terms of its design, but the idea here would be that it has the ability to

transit through the heart and lungs in a smaller device, a 16-French system, but it still allows you to expand the funnel to the 24-French size that the other large-bore [PE] devices are currently utilizing."

In the first-in-human ENGULF study of 25 patients from eight centers, he showed a 23.2% mean reduction from baseline in RV/LV ratio at 48 hours, with no major adverse events and no deaths at 30 days.

Kobayashi said the learning curve for operators using the device is minimal. "I feel very strongly that within three to five cases, you're going to be facile with this particular device," he said.

Kobayashi noted that a larger trial is currently underway, adding "I think we're seeing a renaissance here that we're living through," with regard to the entry of PE devices onto the market.

A month ago, the US Food and Drug Administration gave premarket approval to AlphaVac (AngioDynamics), a catheter-directed mechanical thrombectomy device for PE.

Presenting data on that device in the single-arm, investigational device exemption (IDE) APEX AV trial of 122 patients from 25 centers with acute intermediate-risk PE, Keeling said the mean reduction from baseline in RV/LV ratio was 29% at 48 hours, with a 35.5% mean reduction in clot burden and no mortality at 30 days. The study data formed the basis for the FDA's decision.

"This is a comparable safety and efficacy profile to other catheters in the space," Keeling noted, adding that in regulatory terms, the bar for entry of new advanced therapy PE devices is low.

"We've seen a number of catheters become FDA approved through this process and I think that's good for patients, but I think postmarket registries and postmarket analysis of these catheters, especially when it comes to safety and efficacy, is going to be of utmost importance," he added. "I'm a surgeon, but I also use some of these catheter-based therapies. We should be doing more for a lot of these patients, so I agree with the low bar for entry, but . . . [the FDA is] asking us to monitor these devices postmarket."

**10.Sexuality and Race/Ethnicity Intersect to Affect CV Health: NHANES Data**

For women—but not men—who are part of the LGBTQ+ community, the overall CV health impact posed by being a sexual minority differs depending on their racial/ethnic background, an observational analysis shows.

Moreover, the relationships between sexuality and risk factors like smoking, body mass index (BMI), and blood pressure are distinct across Black, Hispanic, and white sexual-minority populations.

Lead author Nicole Rosendale, MD (University of California San Francisco), told TCTMD that this study is a follow-up to their group's prior analysis, also using the National Health and Nutrition Examination Survey (NHANES) database, that adjusted for race/ethnicity when looking at the influence of sexual identity.

For the new study, published in JAMA Network Open, their calculations instead explored the idea of intersectionality, in this case the overlap between sexual identity and race/ethnicity, when it comes to CV health. "Someone isn't just a single identity or experience that they bring in navigating the world. We have multiple identities that all intersect in our access to power and privilege, as well as discrimination [and other] experiences," Rosendale said.

In medicine, "we're starting to get to that nuance" by recognizing social determinants of health and other related concepts, she said, "but I think it's still in its infancy and so this is a step in that direction."

Indeed, a growing body of research is suggesting that LGBTQ+ individuals face unique stressors that may lead to worse CV health compared with cisgender, heterosexual adults. Bisexual women and gay men, for instance, are about 20% more likely to be diagnosed with hypertension than heterosexual individuals, with bisexual women at higher risk of untreated hypertension. Yet oftentimes sexuality and gender diversity aren't addressed during healthcare encounters.

A key takeaway from their current paper is “the importance of understanding that even within a category like lesbian women or bisexual women, there are differences,” said Rosendale. “Different communities have different needs, so we really do have to individualize and focus on [the question of]: who is the person in front of us and what is their particular need?”

Sexuality Plus Race/Ethnicity

The researchers analyzed data on 12,180 adults (mean age 39.6 years) for the years 2007 to 2016. Half of the survey respondents were male. Most (42.1%) self-reported being white, with 27.0% identifying as Hispanic, 20.2% as Black, and 10.7% as “other” race/ethnicity. Self-reported sexual identity—categorized as heterosexual or sexual minority (ie, lesbian, gay, bisexual, or “something else”)—was available for 45.9% of participants.

The researchers scored each person’s CV health according to the American Heart Association’s Life’s Essential 8 metrics—diet quality, sleep quality, physical activity, exposure to cigarette smoking, body mass index, and levels of fasting blood glucose, total cholesterol, blood pressure—based on the NHANES questionnaire, dietary information, and a physical exam. They adjusted for age, survey year, and socioeconomic status.

Compared with heterosexual females, those who were a sexual minority had worse overall CV health. The link between sexuality and poor CV health was strongest among Hispanic female participants (β −5.9) but it was also seen in Black (β −3.2) and white (β −3.3) females. There was no interaction for the “other” racial/ethnic category. Digging deeper, Black (β −5.7) sexual-minority females had significantly lower overall CV health compared with white heterosexual females, whereas there was only a trend seen for Hispanic sexual-minority females.

Males who self-identified as a sexual minority, however, did not see worse CV health compared with heterosexual males, which remained true across all racial/ethnic categories.

Nicotine use may have driven part of the differences, given that Black sexual-minority females fared worse in this area than their Black heterosexual counterparts (β −16.5). Compared with white heterosexual females, white sexual-minority females had worse scores for nicotine (β −14.2) plus worse metrics for BMI (β −8.2); Hispanic sexual-minority females, compared with their heterosexual counterparts, had worse BMI (β −17.3) and worse blood pressure (β -5.1).

Although there was no difference in CV health scores across racial/ethnic groups for sexual-minority versus heterosexual males, there were some differences within individual racial ethnic/groups. Black sexual-minority males had worse exposure to nicotine (β −13.0) but better BMI (β 13.1) and blood pressure (β 6.8) compared with Black heterosexual males. Hispanic sexual-minority males, meanwhile, had worse nicotine exposure (β −20.1) but better BMI (β 11.0) compared with Hispanic heterosexual males. Diets tended to be healthier among Hispanic and white sexual-minority males compared with their heterosexual counterparts (β 8.8 and 7.9, respectively).

Who is the person in front of us and what is their particular need?Nicole Rosendale

Rosendale said she hopes future research can help get at the "why" driving the differences in women, though one partial explanation is the history of discrimination they've experienced both as people in the world and as patients receiving healthcare.

In the investigators' earlier study of NHANES data, led Billy A. Caceres, PhD, RN (Columbia University School of Nursing, New York, NY), they showed that gay men in fact generally had better CV health than heterosexual men: this presents an opportunity to better understand which health practices and forms of community support might be working well in sexual-minority males, she observed. "How can we leverage that to improve cardiovascular health in total for all men?"

It's not so much that clinicians caring for LGBTQ+ patients need to be asking questions targeted at their sexual and racial/ethnic identity, said Rosendale. Rather, healthcare professionals should "be systematic in their approach [to risk factors] and actively listen to their patients . . . about their experiences in life."

For instance, it is incorrect to assume that just "because someone is a lesbian who's in a stable relationship and has a job and this and that, that they don't necessarily need certain health screenings," she noted.

A "strength-based approach" to counseling patients that highlights how well they're taking care of their health also is powerful, Rosendale added. "Even the fact that they're sitting in front of [you] is a huge step. . . . They've been through a lot, [so] acknowledge that and recognize the strength that it takes to get through and access the care that they need."

## 11. Fetal Medicine Foundation Algorithm Can Predict Preeclampsia

The first-trimester Fetal Medicine Foundation (FMF) screening test predicts 63.1 percent of preterm preeclampsia cases and 77.3 percent of early-onset preeclampsia cases, according to a study published online May 6 in Hypertension.

Paul Guerby, M.D., Ph.D., from Université Laval in Quebec City, and colleagues conducted a prospective cohort study of nulliparous women recruited at 11 to 14 weeks to examine the FMF preterm preeclampsia screening test. Receiver operating characteristic curves were used to estimate the detection rate (sensitivity) and the false-positive rate (1-specificity) for preterm and early-onset preeclampsia based on the FMF screening test and according to criteria from the American College of Obstetricians and Gynecologists.

A total of 7,554 participants were recruited, of whom 97 percent remained eligible after 20 weeks. Overall, 0.9 and 0.3 percent

developed preterm preeclampsia and early-onset preeclampsia, respectively. The researchers found that the detection rate was 63.1 and 77.3 percent for preterm preeclampsia and early-onset preeclampsia, respectively, using the FMF algorithm (cutoff of ≥1 in 110 for preterm preeclampsia), at a false-positive rate of 15.8 percent. The equivalent detection rates would have been 61.5 and 59.1 percent, respectively, using the American College of Obstetricians and Gynecologists criteria, for a false-positive rate of 34.3 percent.

"The FMF preeclampsia algorithm should be prioritized over other currently used algorithms," the authors write.

## 12. Fat-Enlarged Axillary Nodes on Mammogram May Indicate Higher CVD Risk

Fat-enlarged axillary nodes on screening mammograms can predict the risk for cardiovascular disease (CVD), according to a study presented at the annual meeting of the American Roentgen Ray Society, held from May 5 to 9 in Boston.

Jessica Rubino, M.D., from the Dartmouth Hitchcock Medical Center in Lebanon, New Hampshire, and colleagues used electronic medical record data from 907 women (ages 40 to 75 years) without known coronary artery disease who had a routine screening mammogram and cardiovascular risk factors available within one year of the index mammogram (2011 to 2012).

The researchers found that 19.1 percent of women had fat-enlarged nodes (>20 mm in length due to an expanded fatty hilum). Women with fat-enlarged nodes had a high risk for CVD defined by pooled cohort equation (>7.5 percent likelihood of major adverse cardiovascular events [MACE] within 10 years; odds ratio [OR], 2.6; 95 percent confidence interval [CI], 1.5 to 4.2), as well as a higher prevalence of type 2 diabetes (OR, 4.0; 95 percent CI, 2.1 to 7.7) and hypertension (OR, 2.5; 95 percent CI, 1.6 to 4.0). There was also an

association observed between fat-enlarged nodes and a trend toward a higher risk for MACE (OR, 1.7; 95 percent CI, 0.9 to 3.1) and low-density lipoprotein cholesterol (OR, 1.4; 95 percent CI, 0.9 to 2.1).

"Incorporating fat-enlarged nodes into CVD risk models has the potential to improve CVD risk stratification without additional cost or additional testing," Rubino said in a statement. "Fat-enlarged axillary lymph nodes visualized on screening mammography may increase the ability to identify women who would benefit from CVD risk reduction strategies and more intensive risk assessment with coronary artery computed tomography."

## 13. Coronary revascularization and sex differences in cardiovascular mortality after myocardial infarction in 12 high and middle-income European countries


### Abstract

**Background**

Existing data on female sex and excess cardiovascular mortality after myocardial infarction (MI) mostly come from high-income countries (HICs). This study aimed to investigate how sex disparities in treatments and outcomes vary across countries with different income levels.

**Methods**

Data from the ISACS-Archives registry included 22 087 MI patients from 6 HICs and 6 middle-income countries (MICs). MI data were disaggregated by clinical presentation: ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). The primary outcome was 30-day mortality.

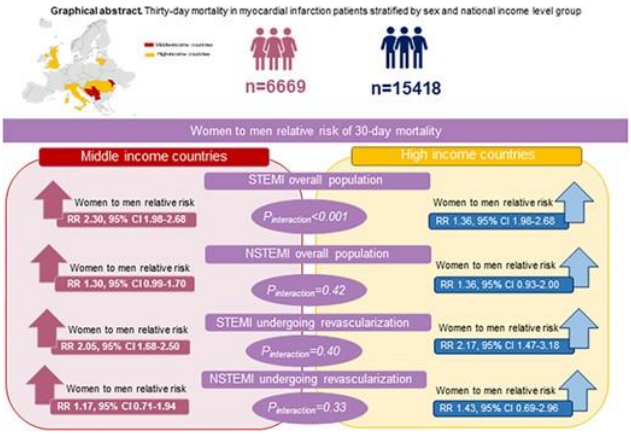
**Results**

Among STEMI patients, women in MICs had nearly double the 30-day mortality rate of men (12.4% versus 5.8%; adjusted risk ratio [RR]

2.30, 95% CI 1.98–2.68). This difference was less pronounced in HICs (6.8% versus 5.1%; RR 1.36, 95% CI 1.05–1.75). Despite more frequent treatments and timely revascularization in MICs, sex-based mortality differences persisted even after revascularization (8.0% versus 4.1%; RR 2.05, 95% CI, 1.68–2.50 in MICs and 5.6% versus 2.6%; RR 2.17, 95% CI 1.48–3.18) in HICs. Additionally, women from MICs had higher diabetes rates compared to HICs (31.8% versus 25.1%, standardized difference = 0.15). NSTEMI outcomes were relatively similar between sexes and income groups.

**Conclusions**

Sex disparities in mortality rates following STEMI are more pronounced in MICs compared to HICs. These disparities cannot be solely attributed to sex-related inequities in revascularization. Variations in mortality may also be influenced by sex differences in socioeconomic factors and baseline comorbidities.




## 14. GENDER DIFFERENCES IN PREDICTORS OF PRIMARY VENTRICULAR FIBRILLATION: RESULTS OF THE PREDESTINATION STUDY

Abstract

Introduction

Few studies evaluated risk factors for ventricular fibrillation (VF) before reperfusion during a first acute myocardial infarction (AMI).

Important parameters such as blood potassium levels (K+), blood pressure (BP) and heart rate (HR) at presentation were not always considered. Furthermore, the potential for gender differences has never been investigated.

Objectives

To evaluate the presence of gender differences in predictors of primary VF development in the PREDESTINATION (PRimary vEntricular fibrillation and suDden dEath during a firST myocardial iNfArcTION) population.

Patients and Methods

PREDESTINATION is a prospective, multicenter, case–control study (matching 1:2 for sex and age) enrolling patients between 18 and 80 years of age with a first AMI, complicated (cases) or not (controls) by primary VF.

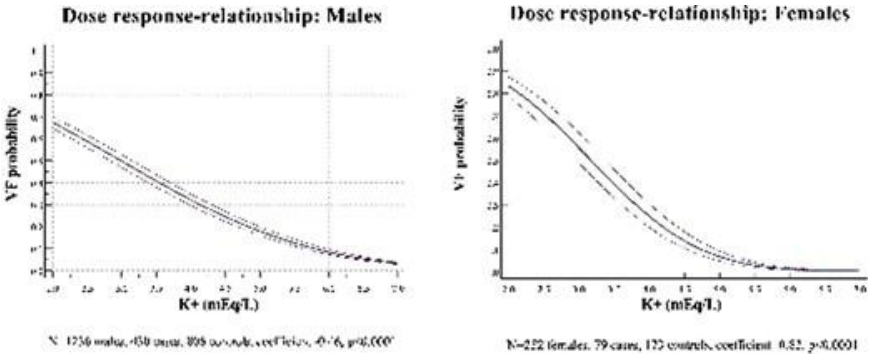
Results

1622 patients were analyzed (average 59 years, 83% male, 35% cases). Comparing male vs female cases, women were older, with lower BMI and lower potassium levels at presentation (3.6 ±0.6 vs 3.8±0.6 mEq/L, p=0.02); they also had a greater prevalence of first degree family history of sudden death (SD), of depression, of physical inactivity, of higher (3–4) TIMI flow in the culprit artery before reperfusion and of VF as first symptom of the AMI (27% vs 15%, p=0.03). The multivariable analysis (logistic regression) performed on the entire population and then only in males identified 9 independent predictors of primary VF, of which 7 risk factors (atrial fibrillation, first K+ ≤3.5 mEq/L, HR ≥90 bpm, family history of SD, anterior site of the AMI, known hypercholesterolemia, physical inactivity) and two protective factors (known diabetes mellitus and higher systolic BP at presentation). Only 2 factors were confirmed in women: first K+≤3.5 (OR 3, 95% CI 1.6–5.8, p<0.001) and systolic BP (OR 0.98 per mmHg, 95% CI 0.97–0.99, p=0.02); depression showed a trend for significance. The dose–response correlation coefficient between kaliemia and the

probability of primary VF was much more negative in women than in man (figure).

Conclusions

The current analysis identified gender differences between cases of primary VF. Only 2 independent predictors of primary VF were found in the female population, with a strong significance of hypokalemia and a much stronger dose–response relationship than in males. These findings aim to start to fill the gap in knowledge of gender specific risk factors for primary VF.




15. **Patient–Physician Sex Concordance and Outcomes in CVD**

The following are key points to remember from a systematic review on patient–physician sex concordance and outcomes in cardiovascular disease (CVD):

1. The sex disparity in outcomes of patients with CVD is well-described and has persisted across recent decades.
2. While there have been several proposed mechanisms to explain this disparity, there are limited data on female patient–physician sex concordance and its association with outcomes.
3. There is emerging evidence of a positive relationship between patient–physician sex concordance and clinical outcomes, particularly among female patients.
4. Equally important is the finding that patient–physician sex discordance is most detrimental to clinical outcome in female patients.

5. The authors review the existing literature on the relationship between patient–physician sex concordance and clinical outcomes in patients with CVD, the evidence of a benefit in clinical outcomes with female patient–physician sex concordance, and the possible drivers of such a benefit and highlight directions for future study.
6. Drivers of a benefit of patient–physician sex concordance in female patients are unclear but may include a greater emphasis on preventive care among female physicians, better and more supportive communication from female physicians possibly leading to improved patient adherence, superior clinical outcomes among female physicians, or the absence of implicit physician bias in sex-concordant patient–physician pairs.
7. The initial data are promising, but they are limited by their retrospective design, by the small number of studies on the topic, by the dearth of female practitioners, and by the low enrollment of female patients in CV studies.
8. Prospective, randomized clinical trials dedicated only to female patients/participants would provide more definitive answers regarding the benefit of sex concordance.
9. While randomized trials on patient–physician sex concordance may be difficult to implement, investigating clinical outcomes with patient–physician sex concordance or whether female leadership increases female patient enrollment, increases female entry into CV subspecialties, or mitigates implicit biases may help optimize clinical outcomes in CVD and improve patient-centered care.
10. Of note, sex is just one factor for which patient–physician concordance may impact clinical outcomes. Early data on patient–physician race concordance in general adult internal medicine have suggested higher patient satisfaction with a race-concordant physician.

## 16. Differences in Donor Heart Acceptance by Race and Gender of Patients on the Transplant Waiting List

IMPORTANCE

Barriers to heart transplant must be overcome prior to listing. It is unclear why Black men and women remain less likely to receive a heart transplant after listing than White men and women.

OBJECTIVE

To evaluate whether race or gender of a heart transplant candidate (ie, patient on the transplant waiting list) is associated with the probability of a donor heart being accepted by the transplant center team with each offer.

DESIGN, SETTING, AND PARTICIPANTS

This cohort study used the United Network for Organ Sharing datasets to identify organ acceptance with each offer for US non-Hispanic Black (hereafter, Black) and non-Hispanic White (hereafter, White) adults listed for heart transplant from October 18, 2018, through March 31, 2023.

EXPOSURES

Black or White race and gender (men, women) of a heart transplant candidate.

MAIN OUTCOMES AND MEASURES

The main outcome was heart offer acceptance by the transplant center team. The number of offers to acceptance was assessed using discrete time-to-event analyses, nonparametrically (stratified by race and gender) and parametrically. The hazard probability of offer acceptance for each offer was modeled using generalized linear mixed models adjusted for candidate-, donor-, and offer-level variables.

RESULTS

Among 159 177 heart offers with 13 760 donors, there were 14 890 candidates listed for heart transplant; 30.9% were Black, 69.1% were White, 73.6% were men, and 26.4% were women. The cumulative

incidence of offer acceptance was highest for White women followed by Black women, White men, and Black men (P < .001). Odds of acceptance were less for Black candidates than for White candidates for the first offer (odds ratio [OR], 0.76; 95% CI, 0.69-0.84) through the 16th offer. Odds of acceptance were higher for women than for men for the first offer (OR, 1.53; 95% CI, 1.39-1.68) through the sixth offer and were lower for the 10th through 31st offers.

CONCLUSIONS AND RELEVANCE

The cumulative incidence of heart offer acceptance by a transplant center team was consistently lower for Black candidates than for White candidates of the same gender and higher for women than for men. These disparities persisted after adjusting for candidate-, donor-, and offer-level variables, possibly suggesting racial and gender bias in the decision-making process. Further investigation of site-level decision-making may reveal strategies for equitable donor heart acceptance.

## 17.Holistic Screening for Preeclampsia in First Trimester Bests Clinical Factors Alone

Screening for preeclampsia in the first trimester with the Fetal Medicine Foundation (FMF)'s model—which considers not only clinical characteristics but also additional factors like biomarkers and ultrasound results—is an effective early means of predicting who will develop the condition, according to the prospective PREDICTION study. Developed in the United Kingdom, the FMF's first-trimester screening test for preeclampsia detected nearly two-thirds of preterm cases, with half the false-positive rate seen with the American College of Obstetricians and Gynecologists (ACOG) criteria, which are based on risk factors like comorbidities, family history, body mass index, and age, as well as maternal medical history.

However, the role of the FMF algorithm continues to be debated, said senior author Emmanuel Bujold, MD (CHU De Québec-Université

Laval Research Center, Canada). To help overcome some of the wariness towards tool, and to see if it might be a good fit for everyday practice in North America, the PREDICTION researchers "decided just to evaluate whether it was working or not."

Their trial, published earlier this month in Hypertension, enrolled exclusively women who'd not yet given birth and thus lacked a maternal medicine history to inform screening—a key group of clinical interest.

Speaking with TCTMD, Bujold said that their new findings aren't surprising, given what was known from prior studies. Still, "we were extremely happy, because now we know that it's working, so women will have the opportunity to have the test," he said. "Now we're looking more at: how we can implement it? How can we make it accessible to all women?"

A necessary quality of a screening tool is that its results inspire patients' trust, something that's especially important in pregnancy, a time when many women don't want to take extra medications that might add risk, Bujold pointed out. With other approaches, "the problem is the very high false-positive rate," he said. Recent research done in Ontario has hinted that "since women do not trust the screening, because the false-positive rate is way too high, most do not take the aspirin."

Laura A. Magee, MD (Addison House, Guy's Campus, London, England), whose own work has also explored the FMF algorithm and other approaches to preeclampsia screening, commented on the PREDICTION results for TCTMD. She, too, said the findings are "consistent with the literature."

"What is fabulous about it is that this has been done by a group not involved in [the FMF algorithm's development], so this is a true external validation of the test in real-world settings across multiple sites. All of those things are important in building our confidence in the fact that the test should work for us," she noted.

Magee said she hopes that this helps to calm debates over whether the FMF model is something worth doing. “We already screen women for preeclampsia in practice. It’s not like: should we start screening? What we really need to be asking ourselves is, why are we sticking with an inferior form of screening [and] why aren’t we using a better form of screening?” Implementation research, though more difficult and perhaps less exciting, is “critically important,” she emphasized. “If it doesn’t come off the shelf and if you don’t make it work for your setting, for your patients, it in many ways doesn’t matter that [the earlier-stage studies] happened.”

What we really need to be asking ourselves is, why are we sticking with an inferior form of screening [and] why aren’t we using a better form of screening?Laura A. Magee

Lead author Paul Guerby, MD, PhD (CHU De Québec-Université Laval Research Center), and colleagues analyzed data for 7,325 nulliparous women who were enrolled across five hospitals between 11 and 14 weeks of gestation and followed until delivery.

At their first recruitment visit, the researchers collected information on maternal age, ethnicity, smoking status, method of conception, and chronic diseases (including hypertension, diabetes, and antiphospholipid syndrome) as well as body mass index and mean arterial blood pressure. The women also gave blood samples and underwent fetal ultrasound. Then, between 3 and 6 months after the expected delivery date, the women’s medical files were examined to obtain gestational age at delivery, birth weight, Apgar score, and details of adverse perinatal outcomes such as gestational hypertension and preeclampsia.

Among them, 65 (0.9%) developed the primary endpoint of preterm preeclampsia with delivery before 37 weeks of gestation and 22 (0.3%) developed early-onset preeclampsia, where the women delivered before 34 weeks.

With the FMF algorithm, the ideal cutoff was ≥ 1 in 110 for preterm preeclampsia, which had a sensitivity of 63.1% and specificity of

15.8%. By comparison, with the ACOG model, sensitivity was 61.5% and specificity was 34.3%. Area under the receiver operating characteristics curve (AUC) for the FMF and ACOG approaches were 0.79 versus 0.64, respectively (P < 0.001).

Using that same cutoff, the FMF algorithm had 77.3% sensitivity and 16.0% specificity. With the ACOG model, those values were 59.1% and 34.5%. The AUC again was greater with the FMF versus ACOG screening (0.89 vs 0.62; P < 0.001).

"The impact of our study on practice suggests that first-trimester screening based on a combination of biophysical, biochemical, and ultrasound variables should be favored over current screening based on clinical risk factors," the investigators conclude. "As aspirin for the prevention of preterm preeclampsia is most effective when initiated before the 16th week of pregnancy, and as nuchal translucency measurement for the screening of aneuploidies is routinely performed in many settings, it would, therefore, be possible to progressively offer this screening in many North American settings."

For decades, there's been interest in the potential for aspirin to prevent preterm preeclampsia, Guerby et al note. "Several national societies now recommend initiating aspirin before the 16th week of gestation in pregnant women identified as high risk for preeclampsia based on the presence of specific single or multiple maternal demographic or medical historical risk factors as part of published checklists. However, this checklist approach is associated with a limited sensitivity or specificity."

The more-holistic FMF algorithm could help aid prevention efforts, the researchers suggest. Using the FMF model, they estimated the number needed to treat (NNT) with aspirin to prevent one case of preterm preeclampsia is 46. By comparison, the ACOG model has an NNT of 101.

Bujold and Magee both noted that the FMF algorithm is already gaining traction in some areas of the world. For instance, the tool is embedded in the astraia software and available on the FMF website.

“There is more and more interest in integrating the approach into clinical practice, and that’s really followed, in particular, the ASPRE trial,” said Magee.

The 2017 ASPRE trial, which showed the benefits of low-dose aspirin in women at high risk for preterm preeclampsia, incorporated the FMF tool as part of its design. The study was done at centers in the United Kingdom, Spain, Italy, Belgium, Greece, and Israel. “From what I’ve heard, many of those centers now keep using it,” said Bujold.

Following their own experience with the 7,300-patient PREDICTION study, he said, the researchers are “trying to repeat a similarly sized study where [after FMF screening] we are giving the aspirin where women are at high risk. We hope to see a decrease of preeclampsia [compared with] a historical cohort.” A goal going forward is to ensure the screening is accessible for all women, even those in lower-income or geographically isolated areas, Bujold added.

Among the barriers to uptake, said Magee, are that the FMF model requires a few extra minutes to do ultrasound and measurement of placental growth factor has an up-front testing cost. “But preeclampsia care costs a lot of money,” she stressed, adding that if the FMF approach to screening were implemented on a wide scale, it would ultimately save money.

## 18.Women, Black and Hispanic Adults Have Lower Angiography/PCI Use in NSTEMI

Disparities are evident in the interventional management of non-ST-segment elevated myocardial infarction (NSTEMI) and in STEMI incidence and mortality, according to two studies presented at the annual meeting of the Society for Cardiovascular Angiography and Interventions, held from May 2 to 4 in Long Beach, California.

Mandvi Pandey, M.D., from Texas Health Resources in Bedford, and colleagues conducted a retrospective analysis of National Inpatient Sample data from 2016 to 2020 for adults with type 1 NSTEMI.

Participants underwent coronary angiography (CA) or percutaneous coronary intervention (PCI) for NSTEMI; gender and racial disparities were examined in interventional management for 2,153,124 NSTEMI patients. The researchers found that compared with men, women had significantly lower adjusted odds of undergoing CA/PCI (adjusted odds ratio [aOR], 0.816); lower adjusted odds of undergoing CA/PCI were also seen for Black and Hispanic versus White patients (aORs, 0.746 and 0.831, respectively).

Fares Ghanem, M.D., from Southern Illinois University in Springfield, and colleagues examined demographic trends in U.S. STEMI hospitalizations using data from 3,426,898 eligible patients. The researchers found that from 2004 to 2020, there was a steady decrease in overall STEMI incidence from 98.7 to 49 per 100,000 inpatient hospitalizations per population, especially among older individuals. In small and medium-sized hospitals, STEMI incidence increased, while in large hospitals, it decreased. In the lower-income population, STEMI incidence and mortality were higher. Mortality declined for individuals older than 85 years and those aged 65 to 84 years, while a slight increase was seen for those aged 45 to 65 years.

"The disparities uncovered by our study emphasize there is a gap in care," Ghanem said in a statement. "We encourage clinicians to focus on providing equitable access to high-quality care through increased education and implementing targeted interventions for vulnerable populations."

## 19.Male, Female V1421 Carriers Face Similar Risk for Heart Failure Hospitalization

Male and female V1421 carriers face a similar and substantial risk for heart failure hospitalization, according to a study published online May 12 in the Journal of the American Medical Association to coincide with the European Society of Cardiology Heart Failure 2024, held from May 11 to 14 in Lisbon, Portugal.

Noting that individual studies have indicated that the amyloidogenic V1421 variant of the transthyretin gene increases heart failure and mortality risk, Senthil Selvaraj, M.D., from the Duke University Medical Center in Durham, North Carolina, and colleagues examined the natural history of disease in carriers across mid to late life. Data were included for 23,338 self-reported Black participants initially free from heart failure; 3.2 percent were V1421 carriers.

The researchers found that 10-year carrier risk increased for heart failure hospitalization by 63 years of age, which was mainly driven by heart failure with reduced ejection fraction; the 10-year all-cause mortality risk increased by 72 years of age. Risk with the variant was only modified by age, but not sex or other select variables, with estimated reductions in longevity varying from 1.9 to 2.8 years at ages 50 and 81 years, respectively. Based on these data, due to the variant, 435,851 estimated U.S. Black carriers between ages 50 and 95 years were projected to cumulatively lose 957,505 years of life.

"Male and female V1421 carriers faced similar and substantial risk for HF hospitalization, predominantly with reduced ejection fraction, and all-cause death later in life, with steep age-dependent penetrance,"

## 20.Pathophysiology of Preeclampsia-Induced Vascular Dysfunction and Implications for Subclinical Myocardial Damage and Heart Failure

### Abstract

Tragically, preeclampsia is a leading cause of pregnancy-related complications and is linked to a heightened risk for morbid and fatal cardiovascular disease (CVD) outcomes. Although the mechanism connecting preeclampsia to CVD risk has yet to be fully elucidated, evidence suggests distinct pathways of early and late preeclampsia with shared CV risk factors but with profound differences in perinatal and postpartum risk to the mother and infant. In early preeclampsia,

<34 weeks of gestation, systemic vascular dysfunction contributes to near-term subclinical myocardial damage. Hypertrophy and diastolic abnormalities persist postpartum and contribute to early onset heart failure (HF). This HF risk remains elevated decades later and contributes to premature death. Black women are at the highest risk of preeclampsia and HF. These findings support closer monitoring of women postpartum, especially for those with early and severe preeclampsia to control chronic hypertension and reduce the potentially preventable sequelae of heightened CVD and HF risk.

## Highlights

- Preeclampsia is a leading cause of pregnancy-related complications and is linked to CVD.
- Mechanisms linking preeclampsia to CVD remain incompletely defined, especially for early vs late onset preeclampsia.
- Preeclampsia is a disorder of the uterine and other arterial beds, with widespread vascular dysfunction.
- Diastolic dysfunction may be common but often understudied in women with early/severe preeclampsia and potential link to near- and long-term HF.

## Introduction

Blood pressure (BP) elevations during pregnancy were historically perceived as benign, to fully resolve with delivery, and without untoward consequences. Recent population series unearth critical links between hypertensive disorders of pregnancy and an elevated hazard for morbid and fatal cardiovascular disease (CVD) outcomes.[1,2] To date, the mechanism linking hypertensive disorders, especially preeclampsia, to elevated CVD risk has yet to be fully elucidated. Providing insight into the near- and long-term CV consequences of preeclampsia is critical given its rising incidence over

the past several decades.[3] We propose to examine evidence as to a role for preeclampsia-induced vascular injury as a potential mechanism for acute maternal and fetal complications during pregnancy but also contributing to subclinical myocardial damage and an evolving risk of heart failure (HF) and other CVD outcomes.

In this review, we discuss potential mechanisms for varied forms of preeclampsia and propose a conceptual model linking early preeclampsia to near-term changes in myocardial function and the long-term sequelae of HF and CVD. Moreover, we synthesize findings regarding vascular maladaptations in preeclampsia in relation to potential pathologic inflammatory and stress-induced milieu that may impact fetal morbidity and mortality during pregnancy and, for the mother, contribute to a heightened CVD risk.

Linking obstetrical findings to the lifelong cardiovascular needs of diverse women embraces the concept of integrated care across specialties facilitating opportunities to create unique care pathways traversing from early detection to reduced long-term CVD risk in women.

## Defining preeclampsia and moderate-high risk women

Preeclampsia is defined as systolic BP ≥40 mmHg or diastolic BP ≥90 mmHg (≥2 occasions >4 hours apart) after 20 weeks of gestation (and up to 6 weeks postpartum) in a previously normotensive patient occurring with proteinuria or end-organ damage (impaired liver function, renal insufficiency, pulmonary edema, new cerebral/visual disturbances, or thrombocytopenia).[4,5] Preeclampsia occurs in ~ 5%-8% of all pregnancies.[6] This would also include women with a prior diagnosis of hypertension who are at elevated risk of preeclampsia. Women with prior preeclampsia, multifetal gestation, chronic hypertension, diabetes, kidney disease, and autoimmune disease (eg, systemic lupus erythematosus) are at high preeclampsia risk.[7] Those

with multiple moderate risk factors are also at high risk of preeclampsia including nulliparity, obesity, family history of preeclampsia, age ≥35 years, in vitro conception, low income, and a personal history of small for gestational age, as defined in U.S. Preventive Services Taskforce.[7] Tragically, preeclampsia is a leading cause of maternal and fetal morbidity and mortality, including intensive care unit admission, cesarean delivery, preterm birth (<37 weeks of gestation),[8] and fetal growth restriction; with even higher rates among Black and economically disadvantaged women.[9] Disadvantaged women are diversely impacted by racism that shapes institutional policy and geographical distribution of resources and opportunities, such as housing, access to health care, and other social determinants profoundly impacting their health.[10]

**Pathogenesis of preeclampsia**

In preeclampsia, there is a failure of the normative processes in which fetal trophoblast stem cells transform into a vascular adhesion subtype to elicit remodeling and angiogenesis of the maternal spiral arterioles into high flow vessels (**Figure 1**).[11] This failure of trophoblasts to transform the maternal spiral arteries results in maladaptive remodeling and compromised blood flow and ischemia to the fetus eliciting the maternal syndrome of preeclampsia.[12] There are detailed reviews on the pathogenesis of preeclampsia.[11,13] We highlight key factors initiating the sequelae of uterine artery dysfunction leading to reduced placental blood flow and fetal hypoxia. In preeclampsia, antiangiogenic, placental soluble FMS-like tyrosine kinase-1 (sFlt-1), and proangiogenic markers, placental growth factor (PlGF), have been well studied.[14] As sFlt-1 increases, PlGF is reduced in preeclamptic women, beginning at 13 to 16 weeks of gestation.[15] The ratio of sFlt-1/PlGF reflects an imbalance of antiangiogenic and proangiogenic proteins and is strongly predictive of near-term preeclampsia.[16]

Research has focused on the pro-inflammatory immune cells and cytokines fostering widespread hyperinflammation (eg, IL-10 and tumor necrosis factor-α).[17] High-sensitivity C-reactive protein is produced in the placenta and exhibits a strong relationship with preeclampsia.[18] This is supported by links between preeclampsia and autoimmune diseases, such as type 1 diabetes[19] and to the higher inflammatory states in obesity.[20] This hyperinflammatory milieu and ensuing cellular and molecular actions culminate in the development of hypertension during pregnancy.

The renin-angiotensin system plays a key role in BP regulation with its components synthesized in the placenta.[21] In preeclampsia, renin, angiotensin-1, and aldosterone are significantly reduced.[22] Women with preeclampsia have an increased sensitivity to the vasoconstrictive effects of angiotensin-II.[23] Moreover, women with preeclampsia have an agonistic autoantibody of the angiotensin AT1 receptor that is responsible for BP control.[24]

Finally, in a normal pregnancy, estrogen levels increase primarily in the placenta[25] and promote angiogenesis and vascular remodeling in the uterine artery.[26,27] In preeclampsia, there is a reduction in estrogen[28] (at 15-29 weeks of gestation) resulting in impaired uterine remodeling contributing to fetal hypoxia and growth restriction.[27]

**Early and late preeclampsia**

Evidence is unfolding that the timing of preeclampsia (ie, early vs late) represents differing subtypes.[29] Early preeclampsia, <34 weeks of gestation, exhibits a pattern of hyperinflammation and abnormal angiogenesis[29] and is referred to as 'placental' preeclampsia.[30] Differences between the preeclampsia subtypes may be explained by differing adaptations to syncytiotrophoblastic (STB) stress. In early preeclampsia, STB stress results from shallow endovascular trophoblast invasion in the spiral arteries leading to

ischemia and inflammatory injury.**31** Early preeclampsia is decidedly higher risk for maternal and fetal adverse outcomes including fetal growth restriction.**32** Risk may be detected using the sFlt-1/PlGF ratio which is highly predictive of early preeclampsia with severe features occurring ≤2 weeks.**33** Among the many maternal characteristics, age >35 years is strongly linked to early preeclampsia.**34**

Late preeclampsia (ie, maternal preeclampsia) occurring with delivery or ≥34 weeks of gestation is more common with a benign perinatal course**30** and is the result of a mismatch between normal maternal perfusion and the metabolic demands of the placenta and fetus leading to STB stress.**34**,**35** It is proposed that late preeclampsia develops due to the duress of pregnancy accentuated by maternal risk factors especially obesity and diabetes where insulin resistance and high glycemic levels contribute to late preeclampsia.**36**

The rising prevalence of preeclampsia over the past few decades has been attributed to an increase in obesity and maternal age.**3** These two features appear to result in divergent pathways of early and late preeclampsia but share common risk factors contributing to postpartum CVD risk.

**Preeclampsia is a vascular disorder**

**Uterine artery remodeling**

In a normal pregnancy, there is a doubling of the uterine artery diameter**37** and >20-fold increase in placental perfusion, resulting from increased cardiac output and trophoblastic influences on the uterine spiral arteries transforming them into larger, low resistance vessels (**Figure 1**).**38** During preeclampsia, the myometrial arteries exhibit a maladaptive response with uterine vasoconstriction and impaired angiogenesis.**39** Vasculopathic abnormalities in preeclampsia are strikingly similar to atherogenesis with arterial wall

hypertrophy, endothelial dysfunction, smooth muscle cell loss, and an acute inflammatory response.**40**

Alterations in blood flow to the placenta can be measured using uterine artery Doppler imaging in the first or second trimester with the results highly predictive of preeclampsia.**41** As impedance falls during pregnancy, the uterine artery pulsatility index (PI) and resistance indices generally decrease. A mean PI >1.45 or bilateral early diastolic notching defines abnormal flow waveforms**42** increasing risk of preterm delivery, abruption, and fetal growth restriction, occurring more among women with early preeclampsia.**34**

**Correlative findings in other vascular beds**

In preeclampsia, endothelial dysfunction leads to vasoconstriction, thrombosis, and hyperinflammation.**43** There is a growing understanding that preeclampsia exerts a systemic response with profound vascular effects on the mother leading to diverse pathophysiologic alterations across multiple organs.

**Cerebral blood flow**

Cerebral and visual symptoms (eg, seizures) are hallmarks of eclampsia, occurring in ~ 1% of pregnancies.**44** With eclampsia, cerebral blood flow velocities increase**45** with reduced cerebral blood flow when compared to normotensive women.**46** In preeclampsia, higher velocities against the thin walls of cerebral vessels increase susceptibility to micro-bleeds and potentially cerebral edema.**47**

**Retinal and ophthalmic artery flow**

Flow resistance indices are similarly increased with mean arterial pressure in the ophthalmic and central retinal arteries.**48** At the time

of delivery, retinal artery diameters are significantly smaller in preeclampsia and may persist for ~ 1 year postpartum.[49]

**Systemic vascular dysfunction**

There are few reports noting that women with preeclampsia have a higher arterial stiffness index[50,51] that may remain elevated for up to 3 years postpartum.[52] In a small series, peripheral arterial tonometry measures of vasoreactivity were markedly abnormal in preeclampsia as compared to pregnant controls.[53] Importantly, sufficiently powered samples are not available but represent critical evidence regarding systemic vascular dysfunction in preeclampsia.

**Coronary imaging**

Beyond acute coronary angiography for spontaneous coronary artery dissection, evidence as to the impact of preeclampsia on coronary vasoreactivitiy is unknown.

**Microvascular involvement**

The microvasculature has also been implicated in preeclampsia.[54] From 1 study, 93 women with preeclampsia underwent measurement of skin microvascular function responses to acetylcholine and sodium nitroprusside at 22 to 34 weeks of gestation.[55] They employed a unique method of transdermal drug delivery—iontophoresis—that does not induce systemic effects. In preeclampsia, an exaggerated increase in endothelium-dependent and independent vasodilatory responses exceeds that of normotensive women.

**Myocardial alterations in preeclampsia**

In the acute phase, the pro-inflammatory state of preeclampsia leads to myocyte hypertrophy, fibrosis, decreased cardiac output, and reduced left ventricular (LV) compliance, especially with early or

severe preeclampsia.**56** There are few robust series during pregnancy but in one report in 4,795 women undergoing echocardiography at 20 weeks of gestation, the greatest predictors of preeclampsia were high total vascular resistance, reduced cardiac output, global longitudinal strain, and left atrial volume.**57**,**58** A strong relationship between sFlt-1 and global longitudinal strain and LV mass has been reported, supporting a connection with early preeclampsia.**59** Similarly, at 24 weeks of gestation in early preeclampsia, there was a high total vascular resistance and low cardiac output with concentric LV hypertrophy and abnormal diastolic filling patterns.**60**,**61** Conversely, late preeclampsia was associated with a low total vascular resistance and high cardiac output with eccentric LV hypertrophy related to an overfilling state but without pressure overload.**34**,**61** Of course, these alterations noted with late preeclampsia may be due to the timing of delivery in the third trimester where total vascular resistance has decreased.

When echocardiography is performed postpartum (with follow-up from 6 months to 18 years postpartum), hallmarks of preeclampsia include diastolic dysfunction, reduced global longitudinal strain, and concentric LV hypertrophy (**Figure 2**).**57**,**62**,**63** At 1 year postpartum, nearly half of women with early**64**,**65** and severe**66** preeclampsia exhibit grade I-II diastolic dysfunction. Worsening diastolic function is reported within 2 years postpartum, is more prevalent with early preeclampsia, and may persist for 10 or more years postpartum.**67** Postpartum follow-up testing is sporadic and a key message from the echocardiographic data is that myocardial damage is prevalent and there is a need for closer monitoring of women postpartum, particularly for those with early and severe preeclampsia.

**Novel imaging of the placenta**

Evidence is emerging as to the role of non-contrast magnetic resonance imaging of placental structure and function, generally in

small samples of women.**68-71** These studies apply varied approaches but document measures reflective of maternal vascular hypoperfusion or oxygenation.**68-71** The placental T2* value may best reflect tissue oxygenation with areas of low-signal intensity reported in the preeclamptic placenta.**68**,**69** The hope is that there would unfold an magnetic resonance imaging phenotype**68** reflecting both structural and functional alterations in perfusion and oxygenation for early detection of preeclampsia.

**Long-term CVD risk**

There is long-term follow-up (~ 15-20 years later) evidence associating preeclampsia with coronary atherosclerosis.**72-74** From one matched cohort, women with prior preeclampsia (~ 14 years postpartum) had slightly more atherosclerosis on coronary computed tomographic angiography (27% vs 20%, *P* = 0.001).**72** Similarly, when compared to age- and ethnicity-matched women, preeclamptic women (ages 40-63 years) developed coronary artery calcium an average of 5 years earlier and exhibited more atherosclerosis progression with aging.**75** What remains unclear is whether preeclampsia leads to early menopause as a mechanism of premature atherosclerosis. One series reported that women experiencing gestational diabetes or hypertensive disorders of pregnancy had an older age at menopause.**76**

Population evidence links preeclampsia to many forms of CVD, but inconsistently to incident myocardial infarction and other ischemic heart disease events.**1**,**50**,**77-81** One key to the elevated long-term risk is the high rate of postpartum, chronic hypertension.**2**,**50**,**77**,**78**,**81-83** From a meta-analysis of >3 million women with 14 years of follow-up, the relative hazard for chronic hypertension was elevated 3.7-fold**2** but was higher among women with early or severe preeclampsia.**2**,**36**,**79** In one report, the risk of premature CVD death by age 60 years was elevated 6.7-fold among women with early preeclampsia.**84**

Several reports reveal a prognostic relationship between preeclampsia and HF; which is the most logical sequelae based on the echocardiographic data.[1,50,85,86] From the Women's Health Initiative (N = 10,292), hypertensive during pregnancy was the lone pregnancy complication associated with HF (OR: 1.8), with a stronger association with heart failure with preserved ejection fraction (HFpEF) (OR: 2.1).[87] In a report from the New York and Florida Healthcare Cost and Utilization Project (N = 2,532,515), the adjusted hazard for HFpEF hospitalization for preeclampsia was 2.1 (model covariates: age, race, diabetes, income, preterm delivery, and others).[88]

HFpEF risk increased early within a few years postpartum at a median age of 34 years.[88] A high relative hazard for HF (4.5) was seen at 1 to 4 years of follow-up among women with severe preeclampsia and eclampsia.[78] This risk attenuated over time but remained elevated 2.6-fold by ≥15 years postpartum, suggesting an evolving but early risk linked to the adverse sequelae of pregnancy[2] and not a graded risk increasing with age, as may be observed with obesity and diabetes in late preeclampsia.

Importantly, HFpEF was highest among preeclamptic Black women.[88] These findings suggest key racial differences that are largely unexplored in the literature.

**Conceptual model of preeclampsia and CVD risk**

There is increasing insight as to novel and divergent mechanisms in early vs late preeclampsia. In early preeclampsia where the uterine artery PI is elevated and fetal and maternal complications are frequent, the existence of systemic vascular dysfunction leading to end-organ injury sets up an early and lifelong risk which appears to elicit diastolic dysfunction and a near-term risk of HF. We propose a conceptual model to characterize distinct pathophysiologic mechanisms as vascular endotypes that exert prominent influences

on CVD risk both during pregnancy and beyond (**Figure 3**). The woman with late preeclampsia has abundant risk factors which would more broadly heighten long-term risk of atherosclerotic CVD. However, we lack many details from an obstetrical history and throughout a woman's life stages to clearly illuminate causal links between preeclampsia and CVD. There is a striking pattern of stress- or hypoxia-induced sequelae of vascular dysfunction that initiates pathologic consequences leading to HF and CVD risk that occur at many stages of a woman's life (**Figure 4**). Perhaps repetitive bouts of vascular injury initially during preeclampsia reflect more broadly an endotype of vascular dysfunction in women.

It is commonly stated that pregnancy can be viewed as a stress test that provides clues as to future CVD risk. As quoted by Williams**89** in describing pregnancy as a stress test for life: "The limited reserves of an impaired organ will be unmasked and the organs fail to increase its function during pregnancy. As a consequence, the already impaired maternal organ can be irreparably damaged…"

**Echocardiography-guided management**

Echocardiography at the time of preeclampsia diagnosis is commonly performed, yet clinical practice guideline recommendations are lacking. We propose a timeline for women with early and more severe preeclampsia which may foster early detection of HF risk (**Central Illustration**). It would seem appropriate that women with early or severe preeclampsia undergo a baseline echocardiogram to assess myocardial (diastolic and systolic) function, including with LV strain. Women with preeclampsia exhibiting early diastolic abnormalities or those with persistently elevated BP despite intensive care should receive serial echocardiographic evaluations to avert the early risk of HF, perhaps beginning at 1 year of follow-up. Moreover, all women with hypertension should have early and regular follow-up for control

of their BP. Particularly, for high-risk women with early or severe preeclampsia, intensified care for control of hypertension should include both pharmacologic intervention and lifestyle modification. Patient education, akin to cardiac rehabilitation, focusing on diet, exercise, and medication adherence will provide lifelong benefits to the preeclamptic woman.

**Concluding remarks**

The field of cardiovascular women's health has mostly ignored the impact of early life triggers for later onset CVD. Tragically, preeclampsia is a leading cause of maternal and fetal morbidity and mortality. Evidence suggests distinct pathways—early and late preeclampsia—with shared CV risk factors yet with profound differences in perinatal and postpartum risk to the mother and infant, both in the near- and long-term risk of CVD. A paucity of evidence exists, especially for high-risk Black women, for postpartum diagnostic and therapeutic strategies of care yet are desperately needed to reduce the near- and long-term sequelae of heightened CVD and HF risk for women with preeclampsia.

## 21.Infertility Treatment Linked to Heart Disease Hospitalization

Infertility treatment is associated with an increased risk for hospitalization due to heart disease, according to a study published in the May issue of the Journal of Internal Medicine.

Rei Yamada, M.D., from Rutgers Robert Wood Johnson Medical School in New Brunswick, New Jersey, and colleagues examined the association between infertility treatment and postpartum heart disease in a retrospective cohort study of patients who delivered between 2010 and 2018 in the United States. The primary outcome was hospitalization within 12 months postdelivery due to heart disease. The rate difference (RD) of hospitalizations was estimated

among patients who conceived with infertility treatment and those who conceived spontaneously.

Infertility was recorded in 0.9 percent of 31,339,991 deliveries. The researchers found that the rates of heart disease hospitalizations were 550 and 355 per 100,000 with infertility treatment and spontaneous conception, respectively (RD, 195; adjusted hazard ratio, 1.99). The most important risk increase was seen for hypertensive disease (adjusted hazard ratio, 2.16). This increased risk was seen as early as 30 days after delivery (hazard ratio, 1.61), with risk increasing progressively up to one year.

"The risks reported here should be interpreted cautiously, considering the low absolute rates of heart disease in the population, including hypertensive disease," the authors write. "However, the findings suggest that providers should consider counseling patients that infertility treatment is a potential sex-specific risk factor for cardiovascular disease."

## 22. Degenerative mitral regurgitation due to flail leaflet: sex-related differences in presentation, management, and outcomes

Abstract

Background and Aims

Presentation, outcome, and management of females with degenerative mitral regurgitation (DMR) are undefined. We analysed sex-specific baseline clinical and echocardiographic characteristics at referral for DMR due to flail leaflets and subsequent management and outcomes.

Methods

In the Mitral Regurgitation International Database (MIDA) international registry, females were compared with males regarding presentation at referral, management, and outcome (survival/heart failure), under medical treatment, post-operatively, and encompassing all follow-up.

Results

At referral, females (n = 650) vs. males (n = 1660) were older with more severe symptoms and higher MIDA score. Smaller cavity diameters belied higher cardiac dimension indexed to body surface area. Under conservative management, excess mortality vs. expected was observed in males [standardized mortality ratio (SMR) 1.45 (1.27–1.65), P < .001] but was higher in females [SMR 2.00 (1.67–2.38), P < .001]. Female sex was independently associated with mortality [adjusted hazard ratio (HR) 1.29 (1.04–1.61), P = .02], cardiovascular mortality [adjusted HR 1.58 (1.14–2.18), P = .007], and heart failure [adjusted HR 1.36 (1.02–1.81), P = .04] under medical management. Females vs. males were less offered surgical correction (72% vs. 80%, P < .001); however, surgical outcome, adjusted for more severe presentation in females, was similar (P ≥ .09). Ultimately, overall outcome throughout follow-up was worse in females who displayed persistent excess mortality vs. expected [SMR 1.31 (1.16–1.47), P < .001], whereas males enjoyed normal life expectancy restoration [SMR 0.92 (0.85–0.99), P = .036].

Conclusions

Females with severe DMR were referred to tertiary centers at a more advanced stage, incurred higher mortality and morbidity under conservative management, and were offered surgery less and later after referral. Ultimately, these sex-related differences yielded persistent excess mortality despite surgery in females with DMR, while males enjoyed restoration of life expectancy, warranting imperative re-evaluation of sex-specific DMR management.