News in October 2023

1. Stark Inequities Plague AVR Rates for Women, Minorities in England

omen and ethnic minorities in England are 25% to 35% less likely than men and white individuals, respectively, to receive valve replacement for aortic stenosis, according to a large national study.

The results are in agreement with similar data from the United States showing that race, sex, age, and socioeconomic status influence AVR rates and access to TAVI, as well as long-held beliefs that aortic stenosis is a male disease, which may be stalling efforts to refer and treat women before decompensation occurs.

“Whether you are in an insurance-based model like the States or whether you're in the [National Health Service; NHS]—where it's free at the point of care—in both healthcare systems we're seeing these disparities,” said Benoy Shah, MBBS, MD (University Hospital Southampton NHS Foundation Trust, England), a co-author of the new study. “So, it can't just be ease of accessing healthcare because you don't have to pay to get treatment in the NHS and this is still an issue.”

When the authors looked at the incidence of timely SAVR or TAVI they found further disparities, with rates of 55% in Black and South Asian patients compared with 65% in white patients.

In their paper, led by Caoimhe Rice, MBBChir, MSc (Corevitas, London, England), Shah and colleagues say the reasons behind the disparities likely fall into three categories: patient-related aspects, factors tied to physicians and healthcare professionals, and issues intrinsic to the healthcare system itself.

“This is very crude, retrospective, zoomed-out data which is giving us a signal,” Shah told TCTMD. “What we really need now are much more specific studies, questionnaires, whatever they may be, that direct questions at patients and doctors and healthcare professionals that are trying to understand some of the factors that could be at play here.”

Longer Wait Times for Women

For the study, published October 3, 2023, in Open Heart, the researchers used the English Hospital Episode Statistics to identify 183,591 adults with aortic stenosis (mean age 79 years). Of those, 31,436 underwent SAVR or TAVI (mean age 72.4 years). A separate cohort included 10,069 adults (mean age 71.3 years) from the Clinical Practice Research Datalink to examine timeliness of AVR.

Compared with men, women were less likely to receive AVR (OR 0.65; 95% CI 0.63-0.66), with similar findings in Black (OR 0.70; 95% CI 0.60-0.82) and South Asian patients (OR 0.75; 95% CI 0.69-0.82) compared with those who were white.

Women also had longer wait times to receiving AVR after seeing a specialist than did men, and they had a greater number of primary care consultations than men prior to AVR.

When patients were categorized by Index of Multiple Deprivation (IMD), those in the top three most-deprived quintiles were significantly less likely to receive AVR than those in the least-deprived quintile ($P < 0.001$ for all comparisons). Additionally, the proportion of timely SAVR or TAVI was 68% in the least-deprived quintile compared with 58% for those in the most-deprived quintile. AVR was considered timely if it was performed electively and without evidence of cardiac decompensation.

Gender Gaps and Cultural Dissonance

For Shah, the data help contextualize the need for clinicians to dig deeper in their discussions with patients to understand how opportunities to intervene are slipping away or being unnecessarily dismissed.

“It could well be that there's just a cultural dissonance between the physician and the patient,” he said. For example, whereas one physician might perceive a patient’s attitude as disinterested, another with knowledge of their culture might be able to “read” the patient better and discuss treatment options rather than continue with medical therapy.

The treatment gender gap is another area where unconscious bias may be creeping in in a number of ways, with male physicians viewing some of their female aortic stenosis patients as frailer than they really are, or assuming that "because they don't complain," they don't need AVR, Shah added.

Then there's what the authors refer to as the "male as default" approach to care, where strong, otherwise healthy male aortic stenosis patients are more likely to be referred for AVR than women, especially by male physicians.

"Let's have a look at the numbers here. Why would it be 30% less likely for women to be offered treatment? It can't be that they were all afraid or they all said they were fine," Shah said. "The way in which you [overcome] that, of course, is by doing what people are trying to do, which is increasing the number of women in medicine, in cardiology, in interventional cardiology."

The authors also say the results illustrate why studies need to broaden their inclusion of underrepresented ethnic groups "to understand how discrepancies in management of aortic stenosis and provision of AVR can be addressed."

2. Validation of Risk Stratification for Cardiac Events in Pregnant Women With Valvular Heart Disease

Background

Most risk stratification tools for pregnant patients with heart disease were developed in high-income countries and in populations with predominantly congenital heart disease, and therefore, may not be generalizable to those with valvular heart disease (VHD).

Objectives

The purpose of this study was to validate and establish the clinical utility of 2 risk stratification tools—DEVI (VHD-specific tool) and CARPREG-II—for predicting adverse cardiac events in pregnant patients with VHD.

Methods

We conducted a cohort study involving consecutive pregnancies complicated with VHD admitted to a tertiary center in a middle-income setting from January 2019 to April 2022. Individual risk for adverse composite cardiac events was calculated using DEVI and CARPREG-II models. Performance was assessed through discrimination and calibration characteristics. Clinical utility was evaluated with Decision Curve Analysis.

Results

Of 577 eligible pregnancies, 69 (12.1%) experienced a component of the composite outcome. A majority (94.7%) had rheumatic etiology, with mitral regurgitation as the predominant lesion (48.2%). The area under the receiver-operating characteristic curve was 0.884 (95% CI: 0.844-0.923) for the DEVI and 0.808 (95% CI: 0.753-0.863) for the CARPREG-II models. Calibration plots suggested that DEVI score overestimates risk at higher probabilities, whereas CARPREG-II score overestimates risk at both extremes and underestimates risk at middle probabilities. Decision curve analysis demonstrated that both models were useful across predicted probability thresholds between 10% and 50%.

Conclusions

In pregnant patients with VHD, DEVI and CARPREG-II scores showed good discriminative ability and clinical utility across a range of probabilities. The DEVI score showed better agreement between predicted probabilities and observed events.

3. Menstruation Linked to Underdiagnosis of Type 2 Diabetes?

Use of A1c levels for the diagnosis of type 2 diabetes in women younger than 50 years may lead to underdiagnosis, owing to the effects of menstrual blood loss on A1c readings, shows the first study of its kind.

The analysis estimates that an additional 17% of undiagnosed women younger than 50 years could be reclassified as having type 2 diabetes, and that women under 50 had an A1c distribution that was markedly lower than that of men under 50, by a mean of 1.6 mmol/mol.

In a study that will be presented at this year's annual meeting of the European Association for the Study of Diabetes (EASD), the researchers wanted to investigate whether a contributing factor to late diagnosis of type 2 diabetes in women under 50 may be the difference in A1c levels due to hemoglobin replacement linked to menstrual blood loss.

The study was published online in Diabetes Therapy, where the researchers note that "If the threshold for diagnosis of diabetes…was lowered by 2 mmol/mol in women under the age of 50, an additional 17% of these women (approximately equivalent to 35,000 women in England and Wales) would be diagnosed with diabetes…, which may contribute to up to 64% of the difference in mortality rates between men/women with diabetes mellitus aged 16-50 years."

They add that A1c levels in women under 50 years were found to be consistently lower than those in men, and with A1c levels in women reaching the equivalent of those in men up to 10 years later, this "may result in delayed diagnosis of diabetes mellitus in premenopausal women."

Noting that the study was observational, senior author Adrian Heald, MD, consultant endocrinologist, Salford Royal NHS Foundation Trust, Salford, United Kingdom, said that "It may be the case that prediabetes and type 2 diabetes in women are not being spotted because the set point needs to be slightly lower, but a systematic study sampling from the population of at risk individuals is needed further to our findings.

"We also need to refer back to use of the glucose tolerance test, because A1c has been used for the past 15 years but it is not the gold standard," added Heald. "Clinicians have often wondered if patients might be missed with A1c measurement, or even overdiagnosed."

Lucy Chambers, PhD, from Diabetes UK, acknowledged that the research was valuable but added that "More research on sex differences in thresholds for a type 2 diagnosis is needed to inform any changes to clinical practice. In the meantime, we encourage clinicians to follow the current guidance of not ruling out type 2 diabetes based on a one-off A1c below the diagnostic threshold."

But in support of greater understanding around the sex differences in A1c diagnostic thresholds, Chambers added, "Receiving an accurate and timely diagnosis ensures that women get the treatment and support needed to manage their type 2 diabetes and avoid long-term complications, including heart disease, where sex-based inequalities in care already contribute to poorer outcomes for women."

4. **US Study: Non-Obstructive CAD Prevalent in Patients with T2MI**

Most patients with type 2 myocardial infarction (T2MI) have non-obstructive coronary artery disease (CAD), as opposed to obstructive CAD, a new study shows.

5. Older Women Who Get Mammograms Risk Overdiagnosis

TOPLINE:

Women who continue breast cancer screening after age 70 face a considerable risk for overdiagnosis.

METHODOLOGY:

- Overdiagnosis — the risk of detecting and treating cancers that would never have caused issues in a person's lifetime — is increasingly recognized as a harm of breast cancer screening; however, the scope of the problem among older women remains uncertain.
- To get an idea, investigators linked Medicare claims data with Surveillance, Epidemiology, and End Results (SEER) data for 54,635 women 70 years or older to compare the incidence of breast cancer and breast cancer-specific death among women who continued screening mammography with those who did not.
- The women all had undergone recent screening mammograms and had no history of breast cancer at study entry. Those who had a subsequent mammogram within 3 years were classified as undergoing continued screening while those who did not were classified as not undergoing continued screening.
- Overdiagnosis was defined as the difference in cumulative incidence of breast cancer between screened and unscreened women divided by the cumulative incidence among screened women.
- Results were adjusted for potential confounders, including age, race, and ethnicity.

TAKEAWAY:

- Over 80% of women 70-84 years old and more than 60% of women 85 years or older continued screening.
- Among women 70-74 years old, the adjusted cumulative incidence of breast cancer was 6.1 cases per 100 screened women vs 4.2 cases per 100 unscreened women; for women aged 75-84 years old, the cumulative incidence was 4.9 per 100 screened women vs 2.6 per 100 unscreened women, and for women 85 years and older, the cumulative incidence was 2.8 vs 1.3 per 100, respectively.

- Estimates of overdiagnosis ranged from 31% of breast cancer cases among screened women in the 70-74 age group to 54% of cases in the 85 and older group.
- The researchers found no statistically significant reduction in breast cancer-specific death associated with screening in any age or life-expectancy group. Overdiagnosis appeared to be driven by in situ and localized invasive breast cancer, not advanced breast cancer.

IN PRACTICE:

The proportion of older women who continue to receive screening mammograms and may experience breast cancer overdiagnosis is "considerable" and "increases with advancing age and with decreasing life expectancy," the authors conclude. Given potential benefits and harms of screening in this population, "patient preferences, including risk tolerance, comfort with uncertainty, and willingness to undergo treatment, are important for informing screening decisions."

LIMITATIONS:

The definition of screening mammography in the study may have misclassified some diagnostic mammograms as screening. Using a more conservative definition of screening mammogram, which largely accounted for this misclassification, estimates for overdiagnosis were smaller, ranging from 15% of cases in the 70-74 age group to 44% of cases in the 85 and older group. Results could not be adjusted for breast density, family history, and other breast cancer risk factors not captured by the data.

6. **ACC CardiaCast: Women are Not Little Men: The Swinging Pendulum of Hormone Therapy**

"Women are Not Little Men" is a new podcast series within CardiaCast designed for cardiovascular health providers to increase awareness of sex-based differences in cardiovascular disease (CVD) and to improve the clinical care of women with CVD. "Women are Not Little Men" is hosted by Drs. Emily Lau and Niti Aggarwal, nationally renowned experts in women's CVD and members of the American College of Cardiology CVD in Women Committee. In this episode, Drs. Chrisandra Shufelt and JoAnn Manson discuss up-to-date evidence on hormone therapy and CVD risk.

7. Cardiac Surgeons Issue 'Call to Action' to Improve CABG Outcomes in Women

An all-female panel of cardiac surgeons issued a "call to action" to a packed house here today to remind the surgical community there is significant ground to cover to improve outcomes in female patients after coronary artery bypass graft surgery.

Speaking at the European Association for Cardio-Thoracic Surgery (EACTS) annual meeting, Rashmi Yadav, MBBS, PhD (Royal Brompton Hospitals, London, England), reminded her audience that "women are not simply small men" and highlighted the myriad ways the community is failing female patients.

"Women are more likely to die, more likely to have worse outcomes, and more likely to have an infection compared with men in coronary surgery," she said.

Referring to recent findings from a Lancet commission aimed at reducing the global burden of cardiovascular disease in women, Yadav pointed out that 35% of all deaths in women are from cardiovascular diseases. Quoting the commission, Yadav reminded the audience that cardiovascular disease remains "understudied, underrecognized, underdiagnosed, undertreated, and women are underrepresented in clinical trials."

In fact, research suggests that the representation of women in CVD trials is declining. In one study, women made up just 20% of participants, but their percentage declined from a high of 29% in 2000 to 13% in 2019.

“There is this real, global data gap in cardiovascular disease in women and the first step to address this and improve the outcomes of coronary surgery in women is research,” said Yadav.

One trial that may close the research gap is ROMA-Women. Mario Gaudino, MD, PhD (Weill Cornell Medicine, New York, NY), one of the principal investigators, said that while there are observational data to support multiarterial grafting over a single arterial graft, this is being put to the test in a randomized trial in the 4,000-patient ROMA trial. Moreover, it remains possible the treatment effect may vary by sex. However, with only a minority of female patients (approximately 15%), ROMA, which has completed enrollment, would be unable to detect meaningful differences between men and women.

Given that concern, investigators took advantage of existing site infrastructure and launched ROMA-Women. Speaking in the EACTS session, Gaudino provided an update on the trial’s progress, noting it recently gained support from the Global Cardiovascular Research Funding Forum, an international consortium of funders for investigator-led multinational trials. To date, the trial has enrolled more than 200 out of a planned 1,300 patients—not including the roughly 700 female participants in ROMA who will be rolled into ROMA-Women—since the trial launched 3 months ago.

That pace of enrollment is “better than expected,” said Gaudino. “If we keep this pace, we can make this impossible trial possible.”

Bleaker Picture Before and After CABG

Cardiac surgeon Sigrid Sander, MD (Medical University of Vienna, Austria), also speaking at the EACTS meeting, painted a bleak landscape.

“When we talk about disparities in outcomes in CABG between women and men, we need to recognize that in the treatment of coronary disease, there is a disparity every step [of the] way—preoperative to postoperative—that contributes to these differences in outcomes,” said Sander.

Women are diagnosed with CAD later than men and are referred later for surgery, at which point they have a larger burden of comorbidities, “all of which contributes to greater baseline risk,” she said. Additionally, women are less likely to be treated with guideline-recommended revascularization techniques, including left internal mammary artery (LIMA) grafting to the LAD, multiarterial grafting, and complete anatomic revascularization. Intraoperatively, women are more likely to experience anemia and are less likely to receive guideline-recommended secondary prevention medications upon discharge, including referrals to cardiac rehabilitation.

“All of this translates into disparities in outcomes,” said Sander. “The majority of the evidence shows that women generally do worse in every measurable outcome.”

In one analysis of more than 1.3 million people undergoing primary isolated CABG between 2011 and 2020, women had higher unadjusted operative mortality and morbidity compared with men every single year. The operative mortality risk attributable to female sex—which is on top of baseline risk—varied from 1.28 to 1.41, with no change over time.

There is this real, durable data gap in women and the first step to address this and improve the outcomes of women is research. Rashmi Yadav

In study after study, Sander showed that women fare worse than men. They have higher risks of graft failure and hospital readmissions, both of which correlate with more clinical events, including MI, revascularization, and mortality. The difference in MACE between men and women after surgery does appear to narrow as patients age, she said, noting one study showed outcomes were similar in patients 75 years and older.

“I think this is related to the different presentation pattern of coronary artery disease, not only between women and men, but also between younger women and those at an older age,” she said. “Younger women frequently present with diffuse disease, which is less amenable to revascularization, whereas older women tend to present with the typical obstructive, epicardial coronary artery disease, which is what we see in men and what we treat very well.”

Bringing Everything to the Table

Speakers in the “call to action” session pointed to keyanatomic and physiological differences that might explain why women fare worse with surgery. They have smaller coronary arteries, even after accounting for body mass index and left ventricular size, smaller conduits, and narrower sternums that make the procedure more technically demanding. The pericardial cavity can also be considerably smaller, an issue when several chest drains are inserted, with the potential to compress the right ventricle when the sternum is closed. Additionally, female sex carries an increased risk of sternal wound infection.

Yadav believes having surgeons who specialize in female CABG patients might go a long way toward improving outcomes.

“Coronary bypass surgery is called a routine operation, but it's far from routine,” Yadav told TCTMD. “It is, perhaps, one of the more technically demanding operations in cardiac surgery. My view is that people who want to operate on difficult or challenging coronary anatomy, or on particular subsets of patients, such as those with diabetes where there are diffusely diseased vessels, or women patients, then they should commit themselves to it. These challenging areas of coronary surgery should be identified as an area of subspecialist expertise.”

She emphasized the need for meticulous attention to detail when operating on females. “I’m always more alert. I make sure my team are more aware.”

There's also evidence that female patients are more sensitive to bedside manner, she said, with women more perceptive to an absence of empathy from their surgeon compared with male patients. "If the patient is afraid or if they're not sure whether they want surgery, this might make the difference between them accepting or declining an operation that would help them live a longer, symptom-free life," said Yadav. Shared backgrounds, being able to speak their language, guiding them empathetically through difficult decision-making processes—all of this factors into optimizing care for patients, she said.

"You have to bring everything to the table," she said.

Jennifer Lawton, MD (Johns Hopkins Medicine, Baltimore, MD), who chaired the new American College of Cardiology and American Heart Association (ACC/AHA) revascularization guidelines, said that while surgeons await results from ROMA and ROMA-Women, there are things they can do to make sure women are primed for the best possible outcome after surgery.

And while ROMA-Women will provide more details, there are some data to support multiarterial grafting in women to improve survival and reduce MACCE. So, for now, "this is something we, as surgeons, can do," said Lawton.

Both the ACC/AHA and European guidelines recommend the LIMA-to-LAD graft, as well as bilateral internal mammary artery (BIMA) grafting in appropriate patients, but the American version includes a provision stating that all treatment decisions around coronary revascularization should be based on clinical indication, "regardless of sex, race, or ethnicity" (class I recommendation). In her own practice, Lawton said she didn't always give the same types of grafts to every patient, but now she approaches every surgery with the aim of performing a BIMA graft and radial artery graft unless contraindicated.

Overall, closing the treating gap isn't insurmountable, said Yadav. "When you start to watch and study something, the results will improve," she said.

8. **How preeclampsia accelerates aging in women**

Preeclampsia—the life-threatening surge in blood pressure that strikes 1 in 25 pregnancies—is an enigmatic condition. Each year, it causes the deaths of more than 70,000 women worldwide. Because scientists do not know what causes it, they lack targeted strategies to treat it.

Delivery, the only available therapy, is not the "cure" it is often made out to be, according to Vesna D. Garovic, M.D., Ph.D., a nephrologist at Mayo Clinic who has devoted her career to studying this common pregnancy complication. "Even after delivery, women can have dangerously high blood pressure for many days or weeks," she says. "And they remain at an elevated risk for cardiovascular and kidney disease decades later."

Through a combination of laboratory experiments and epidemiological studies, Dr. Garovic has shown that women with preeclampsia undergo a state of accelerated aging that propels them down the path of developing age-related conditions such as heart attack, stroke, and kidney failure.

Her research is unraveling a potential mechanism behind preeclampsia that could lead to the first therapeutics designed to treat an underlying cause of the condition. It also highlights the importance of increased screening and treatment for women with a history of preeclampsia.

The clock is ticking

Most preeclampsia research is based on the premise that the disease arises within the placenta, the organ that materializes with each pregnancy to protect and nurture the developing baby. Researchers believe that in preeclampsia, the "diseased" placenta secretes molecules into the mother's circulatory system that cause inflammation and interfere with the formation of new blood vessels, a process known as angiogenesis. They believe that these nefarious molecules cause systemic disease in the pregnant person.

"The Holy Grail of preeclampsia research," says Dr. Garovic, "has been to identify the molecule or molecules of placental origin that are responsible."

For decades, researchers had noticed that placentas delivered from preeclamptic pregnancies often bore signs that they were aging faster than placentas delivered from normal pregnancies. "However, it was counterintuitive to say that preeclampsia was a disease of aging if you're looking at somebody who's 25 years old," Dr. Garovic says.

In fact, many of the molecules that were elevated in preeclamptic pregnancies were well-known markers of senescence, a cellular state that literally means "the process of growing old." Dr. Garovic postulated that senescence may be the pathway by which some women develop preeclampsia. Senescent cells stop dividing, but they do not die and are not always eliminated from the body. Instead, they sometimes accumulate in tissues and secrete harmful molecules.

Using samples and data from the Rochester Epidemiology Project, Dr. Garovic has tracked various signs of aging and senescence in women with and without preeclamptic pregnancies. Together with Mayo Clinic obstetrician-gynecologists Wendy White, M.D., and Yvonne Butler Tobah, M.D., she found that women who have had preeclampsia have a greater number of chronic conditions later in life—and develop these conditions at a much younger age—than those without a history of preeclampsia.

She also teamed up with Mayo Clinic cellular senescence experts James Kirkland, M.D., Ph.D., and Tamara Tchkonia, Ph.D., to show that women with preeclampsia undergo accelerated aging during pregnancy, as demonstrated by the "epigenetic clock." These epigenetic clocks enable researchers to calculate the biological aging of blood and other tissues by measuring the accumulation of methyl tags—which shift over time in any given organism—at hundreds of sites across the genome.

The researchers found that during their pregnancies and at the time of delivery, women with preeclampsia had aged an average of 2.4 years more quickly than women without the pregnancy complication.

The team took a special subset of cells called mesenchymal stem cells—cells found in bone marrow that help make and repair skeletal tissue like cartilage, bone, and fat—from fat tissue obtained during C-sections of preeclamptic pregnancies and grew them in a dish. They found that those preeclamptic, prematurely aging cells did not form the spindly, tubular structures that give rise to the blood vessels necessary to support healthy pregnancies.

Such impaired angiogenesis may create lifelong complications for both the mother and the child. Interestingly, the researchers showed that they could correct this defect by treating the cells with "senolytics," a class of drugs that selectively eliminates senescent cells.

"Unfortunately, the use of senolytics is contraindicated during pregnancy because the process of cell senescence is critical for the development of the embryo," says Dr. Garovic. "But treatment with senolytics can be considered in non-pregnant women with prior histories of preeclampsia to try to turn back their biological clock and potentially reduce their risk of complications in future pregnancies or later in life."

Dr. Garovic holds out hope that new medications being developed in the field of senescence may one day prove to be safe for use during pregnancy, providing more options to women at risk. "The whole field is exploding," she says.

Reducing ramifications

Even if there are no specific treatments available right now to target senescent cells in women with a history of preeclampsia, Dr. Garovic believes research on the associations between this pregnancy complication and future health issues will have a big impact.

Her studies and others are already leading to new guidelines for the screening and treatment of women at risk, with the ultimate goal of improving outcomes and saving lives. For example, Dr. Garovic served on a working group for the American Heart Association examining hypertension in pregnancy and penned

the association's scientific statement, which called for more work to protect women from complications of hypertensive pregnancies and possible post-pregnancy consequences.

"For women who have had preeclampsia, their blood pressure needs to be monitored, their cholesterol needs to be checked, their kidney function needs to be followed. We need to keep track of their BMI and weight and try to manage lifestyle modifications and their health long-term."

VESNA D. GAROVIC, M.D., PH.D.

"First of all, just changing our approach to treating women with these high-risk pregnancies could make a difference," she says. "For women who have had preeclampsia, their blood pressure needs to be monitored, their cholesterol needs to be checked, their kidney function needs to be followed. We need to keep track of their BMI and weight and try to manage lifestyle modifications and their health long-term."

For now, Dr. Garovic continues to track the health outcomes of women enrolled in the Rochester Epidemiology Project with a close eye on the association between preeclampsia and hypertension, coronary heart disease, congestive heart failure, stroke and cognitive impairment. She also just launched a study in a preclinical model of preeclampsia, which will enable her to establish links between the disease, accelerated aging and adverse cardiovascular outcomes quicker than she could by observing human subjects.

"The ramifications of preeclampsia are amazing, in terms of affecting not only women but also their families and their extended families," says Dr. Garovic. "It is really a disease that has major effects on society. If I could change the perception of the disease, and maybe even figure out how to treat it, that would be very gratifying."

9. **International Consensus on Differential Diagnosis and Management of Patients With Danon Disease: JACC State-of-the-Art Review**

Abstract

Danon disease is a rare X-linked autophagic vacuolar cardioskeletal myopathy associated with severe heart failure that can be accompanied with extracardiac neurologic, skeletal, and ophthalmologic manifestations. It is caused by loss of function variants in the LAMP2 gene and is among the most severe and penetrant of the genetic cardiomyopathies. Most patients with Danon disease will experience symptomatic heart failure. Male individuals generally present earlier than women and die of either heart failure or arrhythmia or receive a heart transplant by the third decade of life. Herein, the authors review the differential diagnosis of Danon disease, diagnostic criteria, natural history, management recommendations, and recent advances in treatment of this increasingly recognized and extremely morbid cardiomyopathy.

Highlights

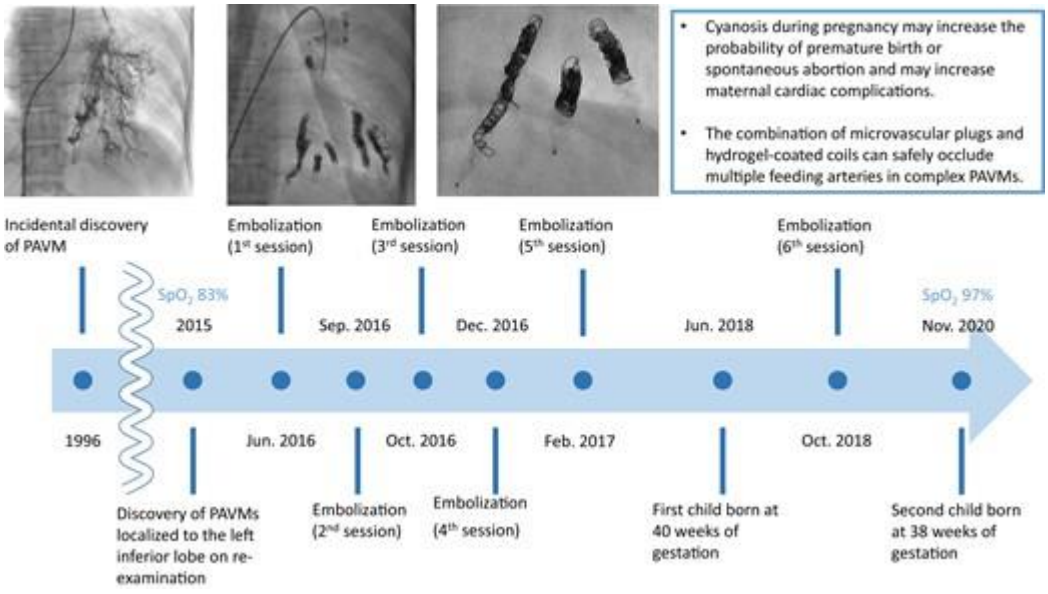
- Danon disease is a rare, X-linked genetic cardiomyopathy in which protein deficiency results in autophagy, accumulation o autophagosomes, defective mitochondria myocyte death, and adverse clinical outcomes.
- Clinical features include myocardial hypertrophy, conduction abnormalities, heart failure, malignant ventricular arrhythmia, and multisystem involvement.
- Understanding the pathophysiology and clinical trajectory of Danon disease may promote earlier diagnosis, risk stratification, and patient selection for medical and gene therapies that may have implications for other genetic cardiomyopathies.

10. **Pregnancy and delivery after percutaneous embolization with a combination of microvascular plugs and hydrogel-coated coils for unilateral diffuse pulmonary arteriovenous malformations: a case report**

Pulmonary arteriovenous malformations (PAVMs) are abnormal communications between the pulmonary arteries and veins; right-to-left shunts

can cause hypoxaemia, emboli to systemic circulation, and brain abscesses. Pulmonary arteriovenous malformations with feeding artery diameters ≥ 2–3 mm, increased measurable size of PAVMs, paradoxical embolism, or symptomatic hypoxaemia are indications for embolization.[1,2] Moreover, cyanosis during pregnancy may increase the probability of premature birth or spontaneous abortion and frequency of maternal cardiac complications; thus, PAVMs should be treated before pregnancy whenever possible.[3,4] We describe a 24-year-old woman with chronic cyanosis and diffuse multiple PAVMs localized to the left inferior lobe, who conceived and carried pregnancy to term after percutaneous embolization with microvascular plugs and hydrogel-coated coils.

Summary figure



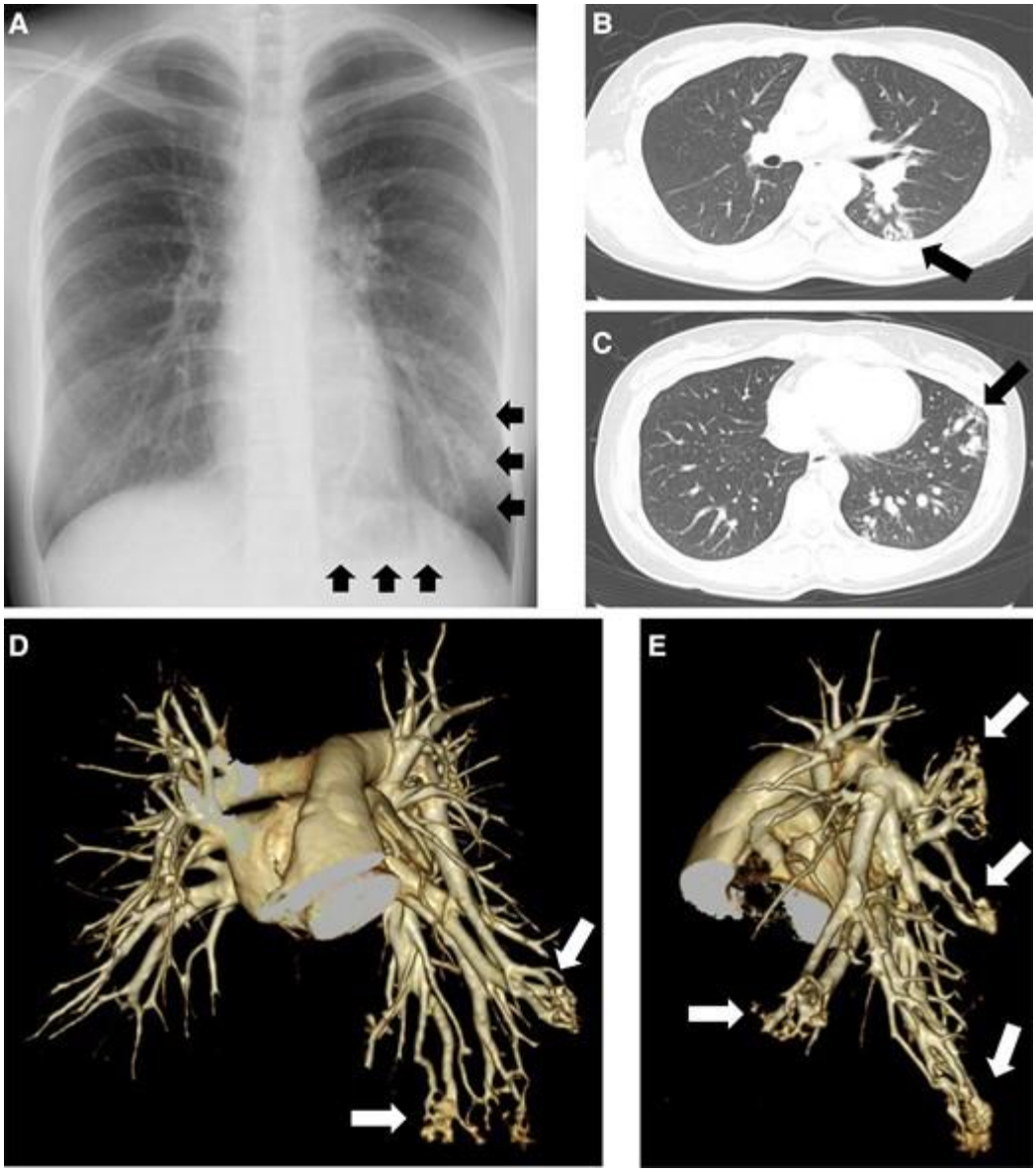
Case presentation

The patient was a 24-year-old woman with PAVMs diagnosed at 1 year of age because of hypoxaemia. She experienced increased exertional fatigue and chronic headaches and had New York Heart Association class II, although her resting sitting peripheral oxygen saturation (SpO_2) remained unchanged at 83% over the past 20 years. She had a history of allergic rhinitis, for which she received antileucotriene agents. She also occasionally used nonsteroidal anti-

inflammatory drugs for chronic headaches. We reconsidered the treatment indications because of the patient desired to conceive.

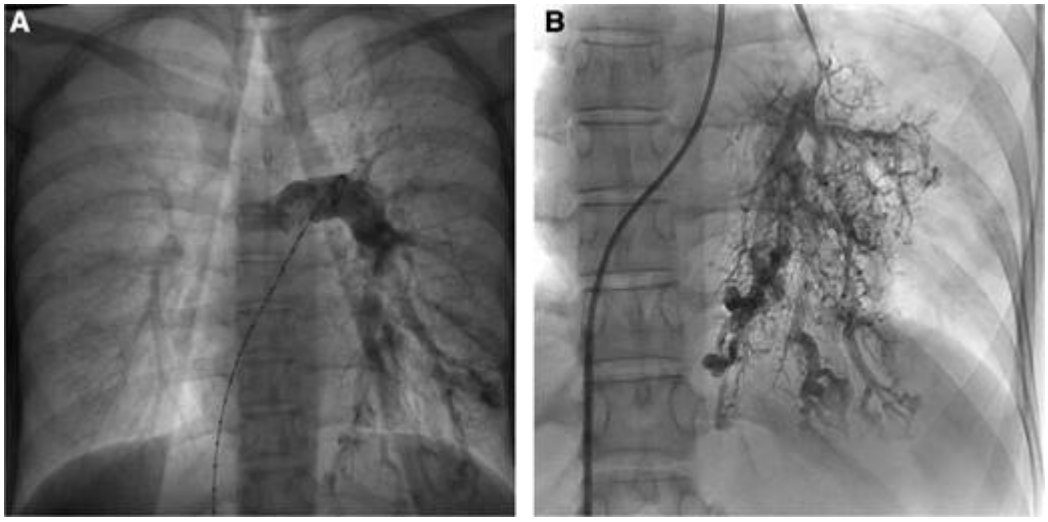
Physical examination revealed cyanosis and digital clubbing. Auscultation revealed normal cardiac and pulmonary sounds. Electrocardiography depicted normal sinus rhythm, whereas echocardiography showed normal biventricular function without any structural abnormalities. Chest radiography and computed tomography revealed PAVMs in the left inferior lobe (Figure 1). Left pulmonary angiography identified diffuse and multiple segmental feeding artery branches measuring 2–4 mm in diameter (Figure 2). All segmental arteries in the left inferior lobe were involved. No obvious lesions were observed in the right or left superior lobe. In the supine position, the arterial blood oxygen saturation (SaO_2) was 91.8% (reference: 94–99%), and partial pressure of arterial oxygen (PaO_2) was 54.3 mmHg (reference: 80–100 mmHg). The mean pulmonary arterial pressure was 11 mmHg. The SpO_2 increased from 89 to 95% after the occlusion test for the descending branch of the left pulmonary artery. The pulmonary arterial pressure remained unchanged. The haemoglobin and haematocrit levels were 17.7 g/dL (reference: 11.6–14.8 g/dL) and 53.2% (reference: 35.1–44.4%), respectively.

Figure 1



Presentation of pulmonary arteriovenous malformations (arrows). A chest radiograph (A), axial computed tomography images (B, C), and 3D reconstruction images (D, E) showing diffuse multiple pulmonary arteriovenous malformations localized to the left inferior lobe.

Figure 2

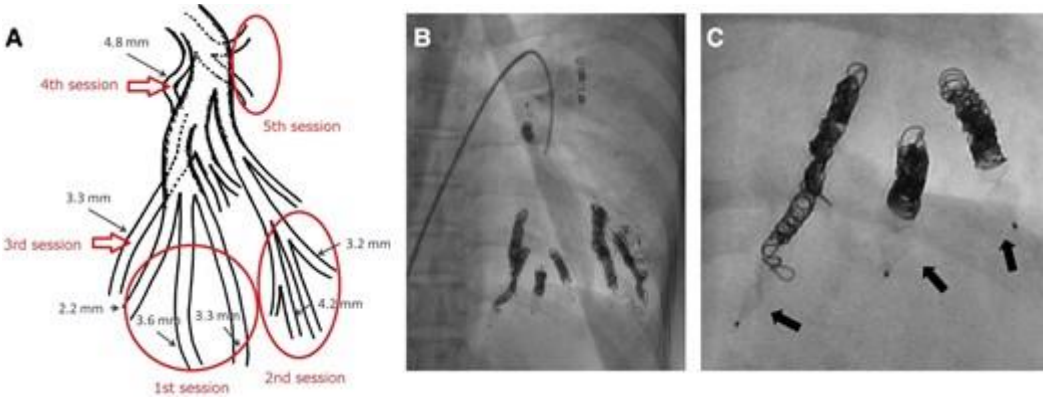


Left pulmonary arteriogram (A) and selective segmental arteriogram of the left inferior lobe (B) in the anteroposterior views showing diffuse multiple pulmonary arteriovenous malformations. Multiple segmental feeding artery branches are identified. All segmental arteries of the left inferior lobe are involved.

Subsequently, five sessions of percutaneous embolization were performed over 8 months (Figure 3) via the femoral vein under local anaesthesia. Heparin 2500 IU was administered intravenously for prophylactic anticoagulation immediately after sheath insertion, followed by an additional dose of 1500 IU hourly. A 4–6-F angiographic catheter with a 0.035-inch-diameter guidewire was advanced into the feeding artery as close to the venous sac as possible. An Amplatzer Vascular Plug 4 (AVP 4; AGA Medical, Plymouth, MN, USA) measuring 130–150% of the vessel diameter size was placed. An Amplatzer Vascular Plug II (AVP II; AGA Medical) was used if the guiding catheter could be inserted into the target site. Subsequently, a microcatheter with a 0.014-inch-diameter guidewire was advanced to the AVP and completely embolized with a hydrogel-coated coil (AZUR Peripheral HydroCoil Embolization System; Terumo Medical Corporation, Tokyo, Japan). Device diameters of 4–7 and 6 mm were selected for AVP 4 and AVP II, respectively. A loop diameter of 2–6 mm and coil length of 4–20 cm were used for hydrogel-coated coils. Overall, 12 AVPs and 29 AZURs were used. No intra-procedural adverse events occurred. However, chest pain and C-reactive protein elevation occurred 6 weeks after the first

session. One week after the second session, chest and back pain, C-reactive protein elevation, fever, and pleural effusion were observed. Mild chest pain occurred 2 days after the third session. All symptoms resolved with antipyretic medications. After the fifth session, oxygenation improved to an SaO_2 of 97.7% and a PaO_2 of 79.4 mmHg.

Figure 3



Percutaneous embolization with microvascular plugs and hydrogel-coated coils. An illustration (A) showing the feeding arteries of pulmonary arteriovenous malformations. The first session targeted the anteromedial basal segment (S7 + S8), the second session the lateral basal segment (S9), the third session the posterior basal segment (S10), and the fourth and fifth sessions the superior segment (S6). Fluoroscopic images (B, C) showing the postembolization state of the left lung. Pulmonary arteriovenous malformations were successfully occluded by microvascular plug embolization, followed by hydrogel-coated coil embolization. A magnified view of the left lung basal area (C) showing hydrogel-coated coils implanted proximal to the microvascular plugs (arrows).

Fifteen months after the fifth session, she delivered her first child. Considering the residual right-to-left shunt, thromboprophylaxis with subcutaneous heparin calcium injection was initiated at 8 weeks of gestation. The exercise test showed SpO_2 of <90%; therefore, oxygen therapy was continued. Antibiotic prophylaxis (cefazolin 1000 mg) was administered during delivery. A 3195 g male infant was born at 40 weeks of gestation without complications. Catheterization was planned for evaluation 1 year after the fifth session but

was postponed to 1 year after birth due to pregnancy. Preprocedural SaO_2 and PaO_2 were 96.5% and 86.2 mmHg, respectively, which had not decreased since the fifth session 2 years ago. The mean pulmonary arterial pressure was 10 mmHg. Pulmonary angiography revealed no evidence of reperfusion or recanalization. The remaining small PAVMs were embolized with AZUR. She conceived again and delivered her second child (birth weight 2895 g) at 38 weeks of gestation, without complications. After 2 years, resting sitting SpO_2 was sustained at 97%.

Discussion

Cyanosis during pregnancy may increase the probability of premature birth or spontaneous abortion and frequency of maternal cardiac complications.[3,4] The 2018 European Society of Cardiology guidelines state that maternal complications are more likely to occur in pregnant patients with cyanosis, and when oxygen saturation is <85%, foetal growth restriction, prematurity, and foetal death are common; thus, pregnancy should be discouraged.[5] Our patient, who desired to bear a child but had chronic hypoxaemia due to PAVMs with feeding arteries of ≥2–3 mm, met treatment criteria and underwent successful percutaneous embolization of these malformations.

Percutaneous embolization is the first-line treatment for PAVMs. Although coils are standard, microvascular plugs were also used in the present case. Our five-point strategy stressed on less invasiveness, lower risk embolus migration to the pulmonary veins, high embolic effect, shorter procedural time, and no reperfusion or recanalization. We chose the combination of microvascular plugs and hydrogel-coated coils for two major reasons. First, microvascular plugs reduce the risk of inadvertent embolus migration to the pulmonary veins and shorten the procedure. Second, hydrogel-coated coils have a strong embolic effect and prevent recanalization and revascularization. Microvascular plugs have a larger diameter than coils and can be implanted as anchors in lesions with rapid blood flow. The advantage of AVP 4 is that it can be implanted using an angiographic catheter and can easily reach the sac. In contrast, hydrogel-coated coils combine a platinum coil with an expandable hydrogel polymer that

swells after implantation and occupies the space between the coils, yielding a greater embolic effect than conventional coils. The main mechanism of action of conventional coils is embolization by thrombus formation; once embolized, the thrombus may dissolve and recanalize. In contrast, hydrogel-coated coils are embolized by swelling of hydrogel, reducing the likelihood of recanalization. Shimohira et al.6 used hydrogel-coated coils in 57 PAVM cases and reported a technical success rate of 98% without recanalization at a mean follow-up period of 19 months. Similarly, a prospective study of 21 PAVM cases managed by venous sac embolization with hydrogel-coated coils reported technical success of 95% without recanalization or reperfusion.7 Trerotola et al.8 reported the embolic effect of microvascular plugs combined with coils. Type 1 AVPs were combined with fibred platinum coils to embolize 39 feeding arteries. An AVP was carefully placed into the feeding artery as close as possible to the venous sac to prevent the risk of recanalization. The procedure was successful for all PAVMs, without recanalization.

In conclusion, percutaneous embolization of PAVMs resulted in safe delivery for both mother and child. Microvascular plugs combined with hydrogel-coated coils produced long-term embolic effects in multiple PAVMs.

11. **Sex Differences in Fractional Flow Reserve– or Intravascular Ultrasound–Guided Percutaneous Coronary Intervention**

Background

A recent randomized trial reported fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) strategy was noninferior to the intracoronary ultrasound (IVUS)-guided PCI strategy with respect to clinical outcomes with fewer revascularizations.

Objectives

This study sought to investigate the sex differences in treatment and clinical outcomes according to physiology- or imaging-guided PCI strategies.

Methods

In this secondary analysis of the FLAVOUR (Fractional Flow Reserve or Intravascular Ultrasonography to Guide PCI) trial, the impact of sex on procedural characteristics, PCI rate, and outcomes according to different strategies and treatment types (PCI vs deferral of PCI) was analyzed. The primary outcome was target vessel failure (TVF) at 24 months, defined as a composite of cardiac death, target vessel myocardial infarction, and target vessel revascularization.

Results

Of 1,619 patients, 30% were women. Compared with men, women had a smaller minimal lumen area, smaller plaque burden, and higher FFR. They had a lower PCI rate (40.8% vs 47.9%; P = 0.008), which was mainly contributed by FFR guidance. Overall, women showed a lower TVF rate (2.4% vs 4.5%). According to the treatment type, the cumulative incidence of TVF was lower in women than in men among those with the deferral of PCI (1.7% vs 5.2%). However, this trend was not observed in patients who underwent PCI. In both women and men, there were no differences in clinical outcomes between the FFR- and IVUS-guided strategies.

Conclusions

In cases of intermediate stenosis, despite receiving fewer interventions, women had more favorable outcomes than men. The use of FFR led to a lower PCI rate but had a similar prognostic value compared with IVUS in both women and men.

12. **Pre-eclampsia**

Pre-eclampsia is a life-threatening disease of pregnancy unique to humans and a leading cause of maternal and neonatal morbidity and mortality. Women who survive pre-eclampsia have reduced life expectancy, with increased risks of stroke, cardiovascular disease and diabetes, while babies from a pre-eclamptic pregnancy have increased risks of preterm birth, perinatal death and neurodevelopmental disability and cardiovascular and metabolic disease later in life. Pre-eclampsia is a complex multisystem disease, diagnosed by sudden-onset hypertension (>20 weeks of gestation) and at least one other associated complication, including proteinuria, maternal organ dysfunction or uteroplacental dysfunction. Pre-eclampsia is found only when a placenta is or was recently present and is classified as preterm (delivery <37 weeks of gestation), term (delivery ≥37 weeks of gestation) and postpartum pre-eclampsia. The maternal syndrome of pre-eclampsia is driven by a dysfunctional placenta, which releases factors into maternal blood causing systemic inflammation and widespread maternal endothelial dysfunction. Available treatments target maternal hypertension and seizures, but the only 'cure' for pre-eclampsia is delivery of the dysfunctional placenta and baby, often prematurely. Despite decades of research, the aetiology of pre-eclampsia, particularly of term and postpartum pre-eclampsia, remains poorly defined. Significant advances have been made in the prediction and prevention of preterm pre-eclampsia, which is predicted in early pregnancy through combined screening and is prevented with daily low-dose aspirin, starting before 16 weeks of gestation. By contrast, the prediction of term and postpartum pre-eclampsia is limited and there are no preventive treatments. Future research must investigate the pathogenesis of pre-eclampsia, in particular of term and postpartum pre-eclampsia, and evaluate new prognostic tests and treatments in adequately powered clinical trials.

13. **A 20-year population study of peripartum cardiomyopathy**

Background and Aims

The epidemiology of peripartum cardiomyopathy (PPCM) in Europe is poorly understood and data on long-term outcomes are lacking. A retrospective, observational, population-level study of validated cases of PPCM in Scotland from 1998 to 2017 was conducted.

Methods

Women hospitalized with presumed de novo left ventricular systolic dysfunction around the time of pregnancy and no clear alternative cause were included. Each case was matched to 10 controls. Incidence and risk factors were identified. Morbidity and mortality were examined in mothers and children.

Results

The incidence of PPCM was 1 in 4950 deliveries. Among 225 women with PPCM, obesity, gestational hypertensive disorders, and multi-gestation were found to be associated with having the condition. Over a median of 8.3 years (9.7 years for echocardiographic outcomes), 8% of women with PPCM died and 75% were rehospitalized for any cause at least once. Mortality and rehospitalization rates in women with PPCM were ~12- and ~3-times that of controls, respectively. The composite of all-cause death, mechanical circulatory support, or cardiac transplantation occurred in 14%. LV recovery occurred in 76% and, of those who recovered, 13% went on to have a decline in LV systolic function despite initial recovery. The mortality rate for children born to women with PPCM was ~5-times that of children born to controls and they had an ~3-times greater incidence of cardiovascular disease over a median of 8.8 years.

Conclusions

PPCM affected 1 in 4950 women around the time of pregnancy. The condition is associated with considerable morbidity and mortality for the mother and child. There should be a low threshold for investigating at-risk women. Long term follow-up, despite apparent recovery, should be considered.

14. **Maternal and Pregnancy Outcomes Following Heart Transplant**

Study Questions:

What is the risk of pregnancy and delivery after heart transplantation?

Methods:

This retrospective cohort study from 2010–2020 reviewed the Nationwide Readmissions Database to compare heart transplant recipients versus nonheart transplant recipients for International Classification of Diseases (ICD)-9/ICD-10 diagnosis and procedure codes pertinent to delivery hospitalizations, comorbid conditions, and outcomes related to the incidence of severe maternal morbidity, nontransfusion severe maternal morbidity, cardiovascular (CV)-related severe maternal morbidity, preterm birth from delivery hospitalization, and readmissions up to 330 days post-partum. Logistic regression analysis adjusted for age, socioeconomics, clinical comorbidities. and type of facility.

Results:

Databases from 31 states were reviewed (total n = 19,399,521; heart transplant recipients n = 150). Compared with nonheart transplant deliveries, heart transplant recipients had a significantly higher risk for all severe maternal morbidity (24.8% vs. 1.7%), nontransfusion severe maternal morbidity (20.8% vs. 0.7%), CV-related severe maternal morbidity (8.5% vs. 0.12%), preterm birth (44.3% vs. 8.0%), pre-eclampsia without severe features (23.8% vs. 3.3%), pre-eclampsia with severe features (8.5% vs. 2.1%), and cesarean delivery (55.2% vs. 32.8%). Heart transplant recipients had higher mean lengths of hospital stay (6.2 vs. 2.7 days), inpatient charges ($63,458 vs. $18,003), morbidity during delivery, and readmission rates within 1 year (26.9% vs. 3.8%; adjusted hazard ratio, 6.03; 95% confidence interval, 3.73-9.75). Of those heart transplant recipients readmitted post-partum within 1 year, 5.7% were associated with heart failure, myocardial infarction, cerebrovascular accident, graft failure or complication, or death.

Conclusions:

Pregnant heart transplant recipients have significantly higher mortality and morbidity rates of severe maternal morbidity, preterm birth, and hospital readmissions compared to nonheart transplant patients.

Perspective:

Females of child-bearing age 18-49 years comprise 8% of heart transplant recipients. This study provides clinicians with evidence-based data to use when discussing the potential risks and outcomes for heart transplant candidates or recipients considering pregnancy. Compared to nonheart transplant patients, heart transplant recipients had 15-fold greater odds of severe maternal morbidity, 28-fold greater odds of nontransfusion severe maternal morbidity, 38-fold greater odds of CV-related severe maternal morbidity, and 7-fold greater odds of preterm birth. Although a limited size of this study, counseling for child-bearing heart transplant patients should include shared decision making regarding these potential risks for both the mother and child.

15. **Sex Differences in Fractional Flow Reserve– or Intravascular Ultrasound–Guided Percutaneous Coronary Intervention**

Background

A recent randomized trial reported fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) strategy was noninferior to the intracoronary ultrasound (IVUS)-guided PCI strategy with respect to clinical outcomes with fewer revascularizations.

Objectives

This study sought to investigate the sex differences in treatment and clinical outcomes according to physiology- or imaging-guided PCI strategies.

Methods

In this secondary analysis of the FLAVOUR (Fractional Flow Reserve or Intravascular Ultrasonography to Guide PCI) trial, the impact of sex on procedural characteristics, PCI rate, and outcomes according to different strategies and treatment types (PCI vs deferral of PCI) was analyzed. The primary outcome was target vessel failure (TVF) at 24 months, defined as a composite of cardiac death, target vessel myocardial infarction, and target vessel revascularization.

Results

Of 1,619 patients, 30% were women. Compared with men, women had a smaller minimal lumen area, smaller plaque burden, and higher FFR. They had a lower PCI rate (40.8% vs 47.9%; P = 0.008), which was mainly contributed by FFR guidance. Overall, women showed a lower TVF rate (2.4% vs 4.5%). According to the treatment type, the cumulative incidence of TVF was lower in women than in men among those with the deferral of PCI (1.7% vs 5.2%). However, this trend was not observed in patients who underwent PCI. In both women and men, there were no differences in clinical outcomes between the FFR- and IVUS-guided strategies.

Conclusions

In cases of intermediate stenosis, despite receiving fewer interventions, women had more favorable outcomes than men. The use of FFR led to a lower PCI rate but had a similar prognostic value compared with IVUS in both women and men.

16. **Sex differences in type A acute aortic dissection: a systematic review and meta-analysis**

Background

In acute aortic dissection (AAD) sex heterogeneity reports are not exhaustive and in part even conflicting.

Aims

To explore sex differences in clinical features, management, and outcomes among patients with type A AAD.

Methods and results

A systematic review and meta-analysis of the literature were conducted for studies (2004–2022) reporting type A AAD sex differences. Among the 1938 studies retrieved, 16 (16 069 patients, 7142 women, and 8927 men) fulfilled all eligibility criteria. Data were aggregated used the random-effects model as pooled risk ratio and mean difference. Due to information reported by considered manuscripts, analysis were performed only among surgically treated type A AAD patients. At the time of hospital presentation type A AAD women were older than men but had lower body mass index (BMI), body surface area (BSA), and creatinine plasma levels. Active smoking, bicuspid aortic valve, and previous cardiac surgery were less common in women while diabetes mellitus was more frequent. Furthermore, women experienced more frequently pericardial effusion/cardiac tamponade than men. Interestingly, in-hospital surgical mortality did not differ between sexes [risk ratio (RR), 1.02; 95% confidence interval (CI), 0.53–1.99; P = 0.95], whereas 5 (RR 0.94; 95% CI: 0.92–0.97; P < 0.001) and 10-year survival (RR 0.82; 95% CI: 0.74–0.92; P = 0.004) was higher among men. A descriptive analysis of in-hospital outcomes among medically treated type A AAD patients confirmed prohibitive high mortality for both sexes (men 58.6% vs. women 53.8%, P = 0.59).

Conclusions

A female sex phenotype appears to be evident in type A AAD implying the need for a personalized management patient approach along with tailored preventive strategies.

17. Dear Cardiologist: Think You Don’t Belong in Cardio-Reproductive Conversations? You’re Dead Wrong

As I stood on the “Heart2Heart” stage at the annual American College of Cardiology (ACC) conference in New Orleans, LA, last spring, I couldn’t help but feel the weight of my topic at this moment in history. I was invited as a panelist to discuss cardio-reproductive health and the recent legal overturning of the constitutionally protected right to access abortion in the Dobbs v Jackson

Women's Health ruling, and how that may impact the lives of countless people hoping to start a family, or facing an unplanned or unwanted pregnancy. This all comes at a time when the United States is already facing a crisis in maternal health: as pregnancy deaths decline around the world, the US is bucking the trend by seeing maternal mortality tick upwards.

Then, during the panel discussion, a member of the audience raised a hand, asking: "Why should cardiologists even be involved in these conversations?"

Embedded in that question is the stark disconnect between cardiologists and maternal health specialists, calling attention to the urgent need to bridge that gap: no mother should ever go into childbirth fearful that the cost of bringing in a life will be the loss of her own.

So why should cardiologists be involved?

At its foundation, maternal morbidity and mortality is a cardiovascular problem—this should be the fundamental thought when approaching this crisis. Maternal health and cardiovascular health are intricately linked. According to the US Centers for Disease Control and Prevention, cardiac and coronary conditions are among the leading causes of pregnancy-related deaths, despite being largely preventable. In fact, it's the leading cause for non-Hispanic Black women, going back decades. This should come as no surprise since many of these women live in maternity care deserts, which oftentimes are also contraceptive deserts and cardiology deserts, a situation that highlights more than ever that one's zip code truly dictates not just maternal choice, but health outcomes.

Indeed, when we think about maternal health, we often focus on the immediate concerns of pregnancy and childbirth; however, the journey to motherhood starts long before conception. With a scarce number of patients actually undergoing the strongly recommended preconception counseling, many women may have preexisting congenital or acquired cardiovascular conditions, or more commonly cardiometabolic risk factors that go undetected until they become pregnant.

First and foremost, cardiologists play a crucial role in identifying these risks. After all, this is what we traditionally do on nearly every patient we encounter. Unfortunately, we tend to consult with patients later in life, oftentimes not having the opportunity to see, think about, or assess patients of reproductive age. If more of us worked with patients earlier in their life course, or better yet were trained about the full spectrum of factors that influence an individual's health through all stages of their life, then the processes engrained in us would more easily and effectively be routine for these young, at-risk women.

Secondly, the effects of pregnancy on the cardiovascular system can be profound. The increased demands on the heart and circulatory system of pregnancy are often referred to as nature's first cardiac stress test. Who better to deal with a cardiac stress test than a cardiologist?

Additionally, with pregnancy also a window to future health and disease where any increased risk identified in pregnancy and the immediate postpartum may be carried and exacerbated even decades later, cardiologist can play a vital role. As an example, if a patient were to present to my clinic and upon my probing relays to me that 20 years earlier they had an adverse pregnancy outcome (APO), including a hypertensive disorder of pregnancy, gestational diabetes, preterm labor, placental abruption, and/or small for gestational age infant, I'd have to tell them this places them at a twofold greater lifetime risk for heart attack, stroke, and death. I'd thereafter after have to screen for any additional cardiometabolic risk factors, while counseling about risk prevention. Obtaining such a history of APOs is most valuable in reproductive age women prior to the development of the more conventional risk factors.

Unfortunately, more times than not, cardiologists overlook the importance of incorporating such detailed pregnancy history in routine encounters due to the limited emphasis on this aspect during their training and an underappreciation of its significance in common clinical practice. For similar reasons, it's extraordinarily rare for patients, unless asked, to ever reveal such information. Despite several awareness campaigns, this information is currently not public knowledge, chiefly as it's not regularly emphasized by their

obstetrician/gynecologist (OBGYN), leaving patients unaware of this critical health link.

Given all that, truly how best can we as cardiologists be incorporated into maternal healthcare? Perhaps the first step is by simply acknowledging we are an important part of the multidisciplinary, maternal health team. The cardio-obstetric models that have proven to be the ideal, thus far, and have included a team of maternal fetal medicine specialists, OB-GYNs, cardiologists, primary care clinicians, nurse care coordinators, and at times doulas and/or midwives working together.

I'm not naive to the practical constraints and challenges of implementing such cardio-obstetric models, but we must at least understand the value of working in partnership within a reliable network of physicians in each of these various subspecialties to allow easy communication and collaboration on mutual patients. By doing something as rudimentary as that, we can ensure that every pregnant person has access to the care and support they need for a healthy and fulfilling life, not just during pregnancy but throughout their journey into motherhood and beyond, even in settings where dedicated multidisciplinary teams may not be readily accessible.

For me, the audience member's question at the ACC conference was an eye-opener. Still, my answer to their question is simple: we are more important now than ever.

We can be the catalyst that recognizes risk early and therefore can mitigate these risks over time. We are the ones who can help the patients with preexisting acquired or congenital cardiovascular conditions—either by counseling them about what's at stake or fixing the problems that would be putting them at risk. We are the ones who can best risk stratify patients with APOs prior to their development of conventional risk factors, and potentially eventual cardiovascular disease.

If done correctly, cardiology involvement in maternal health has the potential to be one of the most high-yield interventions we have thus far to improve these

astounding outcomes and ultimately combat this crisis. As cardiologists we have to support the education and infrastructure of women's cardiovascular programs, which are both cost-effective and highly beneficial. Even more importantly, as individuals we have to understand that maternal health profoundly affects everyone by encompassing not only the well-being of expectant mothers, but also impacting families, communities, and the healthcare system as a whole.

Active involvement in addressing this crisis and implementing strategies to mitigate it start with the basics of asking the right questions and seeing ourselves as active players in often times uncharted territory. In the end, it's getting more comfortable with the sometimes-uncomfortable conversations centered on reproductive and maternal health, as to provide more comprehensive and patient-centered care. By enhancing our understanding of our patients' unique cardiovascular challenges and experiences during varying life stages, we can truly become better cardiologists and strong guardians for our women, families, and communities.

18. Female Residents From Underrepresented Groups Face Assessment Bias

Female residents in emergency medicine who are also from underrepresented minorities score worse on performance assessments than their white male counterparts, according to a new study published in JAMA Network Open.

Investigators studied assessments of nearly 2700 emergency medicine residents and found disparities between female residents from groups underrepresented in medicine (URM). The disparities are considered discrimination, preventing minority trainees from advancing in their careers, study authors wrote.

The study highlights the need to address the "ongoing and pernicious problem of assessment bias in graduate medical education," said co-author Eric Holmboe, MD, an adjunct professor of medicine at Yale University.

The findings may explain why there are fewer women, people of color, and people from marginalized communities in leadership roles in medicine, said

Diana Lautenberger, MA, director of Gender Equity Initiatives at the American Association of Medical Colleges (AAMC).

Conversations about bias often overlook how assessments impact residents' careers, she said. "We often think of 'bias' interpersonally but pay less attention to evaluations. Yet the evaluation has a dramatic and profound impact on the progress of one's career."

Expanding on Past Research

Previous studies showed racial and gender disparities in standardized resident milestone assessments for internal medicine and emergency medicine, with female or URM residents "consistently rated as less skilled than their male and non-URM counterparts," study authors write. But those studies addressed racial and gender disparities separately.

The authors of the current study used the Accreditation Council for Graduate Medical Education (ACGME) Milestones data for academic years 2014-2015 through 2017-2018 to research "sex-specific ethnoracial discrimination" in assessments of emergency medicine residents.

The ratings were based on standardized Milestones linked to resident demographic data, including ethnoracial identity, binary sex, and Step 2 CK United States Medical License Examination scores that AAMC provided to ACGME. Milestone assessments in EM are conducted twice during the academic year and are grouped into six core ACGME competency areas: patient care, medical knowledge, systems-based practice, practice-based learning and improvement, professionalism, and interpersonally and communication skills.

The study involved 128 ACGME-accredited programs with more than 16,000 assessments and 2708 emergency medicine residents. Of the residents, about 70% were in 3-year programs and nearly 30% in 4-year programs.

The residents in the study were divided into three ethnoracial groups: Asian, URM, and White. Most residents were White (74%), followed by Asian (18%), Hispanic or Latino (8%), and African American or Black (6%). About 35% were women and 14% URM.

19. ACC CardiaCast: Women are Not Little Men: Exploring Arrhythmias in Women

"Women are Not Little Men" is a new podcast series within CardiaCast designed for cardiovascular health providers to increase awareness of sex-based differences in cardiovascular disease (CVD) and to improve the clinical care of women with CVD. "Women are Not Little Men" is hosted by Drs. Emily Lau and Niti Aggarwal, nationally renowned experts in women's CVD and members of the American College of Cardiology CVD in Women Committee. In this episode, Drs. Annabelle Volgman and Kamala Tamirisa discuss sex differences in arrhythmias, including atrial fibrillation and ventricular tachyarrhythmias, as well as gender disparities related to medical and device therapies for arrhythmia treatment.

20. **Women, lipids, and atherosclerotic cardiovascular disease: a call to action from the European Atherosclerosis Society**

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in women and men, and its incidence continues to increase as the pandemics of obesity and cardiometabolic disease escalate.1–3 Among adults <65 years, men have higher absolute ASCVD event rates than women, but in Europe and the USA, the fastest relative increase in ASCVD mortality is in middle-aged women (45–64 years).1,2 Thus, a focus on ASCVD risk in women is important.

Missed or delayed diagnosis and undertreatment of ASCVD are key contributors,4,5 with evidence that women are less likely than men to receive guideline-recommended preventive therapies.6–10 Familial hypercholesterolaemia (FH) exemplifies this. Global data11 show that women are diagnosed later and undertreated, and with time-off lipid-lowering therapy (LLT) during pregnancy and breast feeding, have greater cumulative cholesterol exposure than men with FH,12 possibly explaining why the relative impact of FH on cardiovascular risk is higher in women than men.13,14 The effects of traditional and risk-enhancing factors also differ in women vs. men.15,16 Sex-

specific factors such as pregnancy-related complications, polycystic ovary syndrome (PCOS), and premature menopause also adversely influence cardiometabolic risk factors and impact atherosclerosis progression.[17–19] Evaluating women for cardiovascular risk, ideally from midlife,[20] would improve early identification of those with elevated modifiable risk factors or sex-specific risk factors, and prompt early initiation of guideline-recommended treatment.

This European Atherosclerosis Society (EAS) position statement is a 'call to action' for improving ASCVD prevention strategies in women, with a focus on sex differences in lipids over the life course. The panel acknowledges that while 'female' refers to an individual's biological sex, and 'woman' refers to an individual's gender identity, historically these terms have been used interchangeably in the literature. Therefore, this statement uses the term 'women' for consistency.

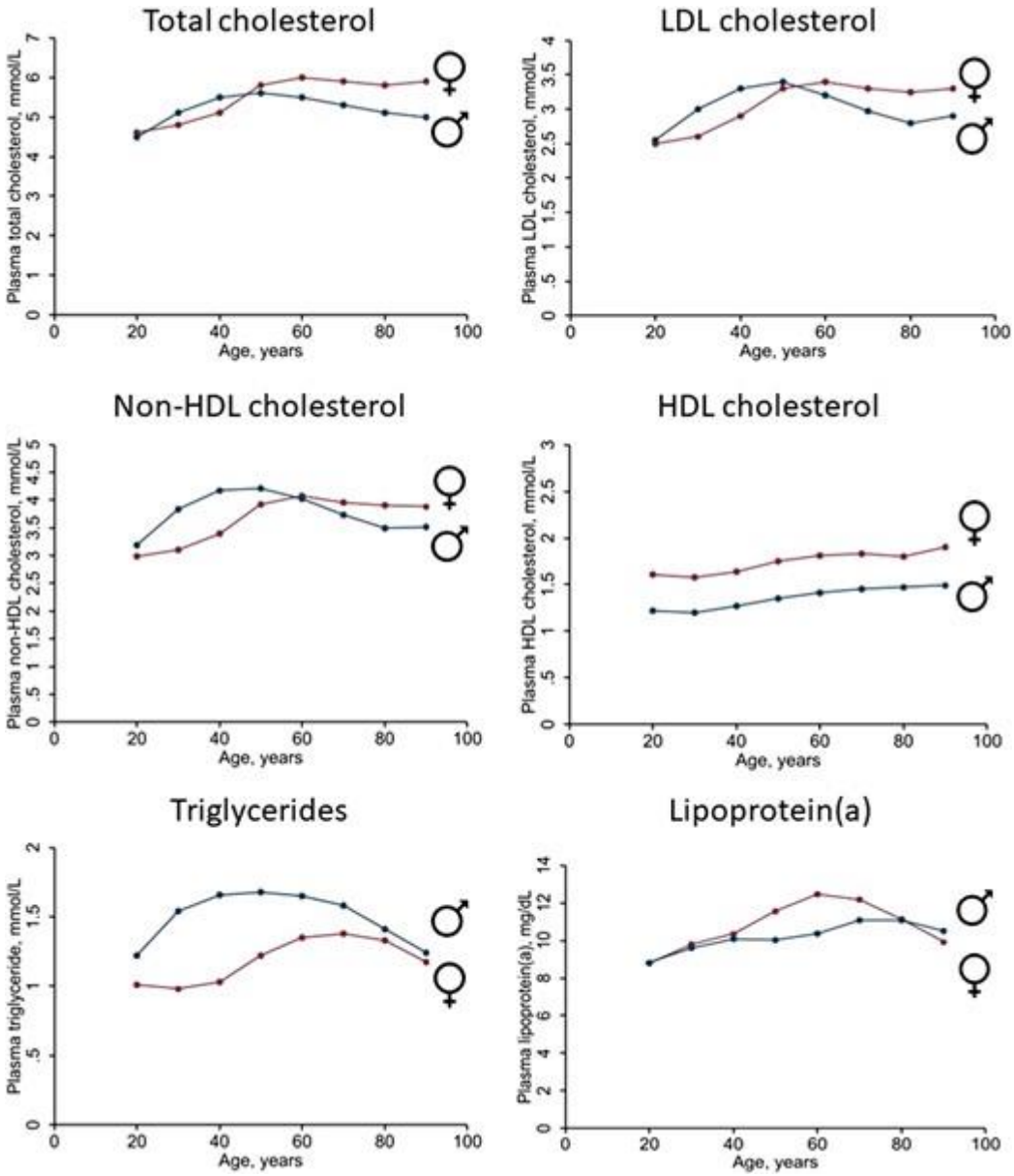
Do cardiovascular risk factors differ in women?

While both sexes share many of the traditional cardiovascular risk factors, the impact of these may differ in women vs. men.[21] For example, although more prevalent in men,[22] diabetes confers a greater relative (although not necessarily absolute) increase in cardiovascular risk in women vs. men of all ages.[23–27] In part this may relate to greater adiposity and more cardiovascular risk factors in women than men at the time of diagnosis,[27–29] as well as sex-specific risk factors for diabetes (e.g. PCOS and gestational diabetes).[27] Women are also typically less physically active and have a higher body mass index (BMI) than men,[30] which is known to associate with ASCVD risk.[31]

Disentangling the effects of declining oestradiol levels at menopause from ageing is difficult and much debated. Most of the large longitudinal studies with measurements before, during, and after menopause transition show changes in cardiovascular risk factors including weight gain, visceral adiposity, adverse effects on lipids (Figure 1),[32] and increases in inflammatory markers and blood pressure, especially systolic blood pressure.[33–37] Whether these changes also

associate with increased risk for ASCVD is more contentious. Two longitudinal studies (249 and 890 subjects)[38,39] reported progression of carotid intima-media thickness (CIMT) related to the menopause, independent of baseline age, although another study (up to 3892 subjects) showed no association between menopausal transition and CIMT progression.[37] This latter study did, however, suggest that increasing adiposity and blood glucose with menopausal transition may impact diabetes risk.[37] Added to this, premature menopause was shown to be associated with an increased relative risk of incident ASCVD compared with similarly-aged women without premature menopause, especially in those with premature ovarian insufficiency with menopause before the age of 40 years.[18,40,41] Women with PCOS have an increased relative risk of cerebrovascular events but not of ASCVD events.[19]

Figure 1

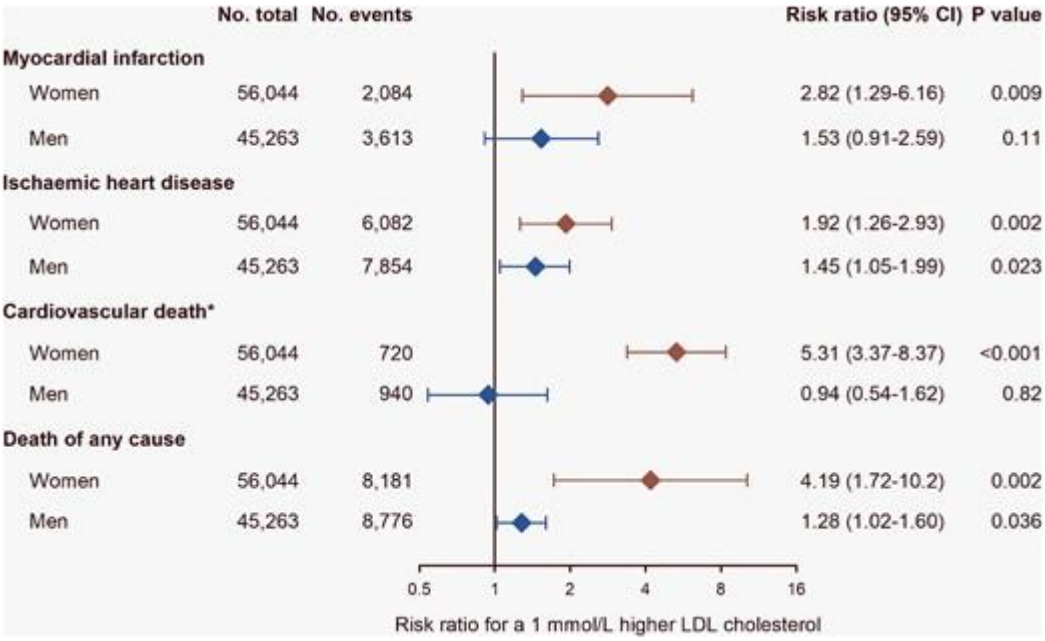


Mean non-fasting plasma levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, non-high-density lipoprotein (HDL) cholesterol, HDL cholesterol, triglycerides (TGs), and lipoprotein(a) [Lp(a)] based on data from 59,278 women and 48,314 men in the Copenhagen General Population Study. Plasma levels of total cholesterol, HDL cholesterol, and TG were measured using standard hospital assays (Konelab, ThermoFisher Scientific, Waltham, Massachusetts, USA). The LDL cholesterol was calculated using the Friedewald equation if TG was ≤4 mmol/L (≤354 mg/dL) or measured directly. Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol. The Lp(a) was analysed with different assays over time, all calibrated corresponding to values using the Denka assay on fresh samples. Samples were either fresh or

stored at −80°C before measurement. Tests for interaction were performed by inclusion of two-factor interaction terms between age and sex in the linear regression model on TG and plasma Lp(a) using a likelihood ratio test between models excluding and including the interaction term. P-value for interaction between age and sex on plasma TG = 3×10^{-207}; on plasma Lp(a) = 5×10^{-8}. To convert cholesterol from mmol/L to mg/dL multiply by 38.7. To convert TG from mmol/L to mg/dL multiply by 88.6. To convert Lp(a) in mg/dL to nmol/L: Lp(a), nmol/L = 2.18 × Lp(a), mg/dL − 3.8332

It has been suggested that low-density lipoprotein cholesterol (LDL-C) is less important as a determinant of ASCVD risk in women vs. men given their lower risk of ASCVD, specifically myocardial infarction (MI), reported in some observational studies.42 However, in the World Health Organization CVD Risk Chart Working Group report, both sexes had similar risk for fatal and non-fatal MI, coronary heart disease (CHD), and stroke per 1 mmol/L increase in total cholesterol.43 Data from the Copenhagen City Heart Study and the Copenhagen General Population Study also showed comparable causal genetic effects of LDL-C on risk for MI and ischaemic heart disease (IHD) in both sexes (Figure 2).44,45 These findings therefore support a similar causal effect of LDL-C on cardiovascular disease in women and men.46

Figure 2



Causal effect of a 1 mmol/L (38.7 mg/dL) higher low-density lipoprotein cholesterol (LDL-C) level on risk for myocardial infarction, ischaemic heart disease, cardiovascular death*, and death from any cause in women and men in the general population, the Copenhagen City Heart Study, and the Copenhagen General Population Study. Data were estimated using Mendelian randomization with a weighted allele score of LDLR (rs267607213, rs121908025, and rs138947766), PCSK9 (rs11591147, rs148195424, rs562556, and rs505151), and HMGCR (rs17238484) using instrumental variable analysis.44,45 The strength of the genetic instrument (i.e. the strength of the association of the genotypes with LDL-C) was similar in women and men (F-statistics 70.8 in women and 67.8 in men). *Cardiovascular death was defined as the primary cause of death. No., number; CI, confidence interval

Sex-specific factors in women merit consideration.47,48 In US guidelines, factors such as pre-eclampsia and early menopause are regarded as 'risk-enhancing' with recommendation for statin therapy in women otherwise at borderline or intermediate risk.49 The 2021 European Society of Cardiology (ESC) Prevention guideline recommends screening for hypertension and diabetes in women with a history of pregnancy-induced hypertension, PCOS, and gestational diabetes.16 Women are also disproportionately at risk of chronic kidney disease, itself a risk factor for ASCVD,16 which presents earlier than in men.50 Auto-immune inflammatory diseases,15 which impact women more than men increasing risk for premature ASCVD51,52 independent of traditional risk factors,53–59 are also considered 'risk-enhancing' factors by guidelines (Table 1).16,49,60

Table 1

Cardiovascular risk in women: what to consider?

- Diabetes: greater impact on cardiovascular risk in women vs. men

- Sex-specific risk factors (pregnancy complications including gestational diabetes and hypertensive disorders of pregnancy, polycystic ovary syndrome, and early menopause)

- Risk-enhancing factors (e.g. chronic kidney disease and auto-immune inflammatory disease): more prevalent in women than men

- Impact of the life course on the lipid profile

- Cumulative cholesterol exposure: in familial hypercholesterolaemia, greater cumulative cholesterol exposure in women is exacerbated by discontinuation of treatment during pregnancy and breastfeeding

- Hormonal and chromosomal effects influencing ASCVD progression
- Women with non-obstructive coronary artery disease may have significant atherosclerotic plaque

Gender

Sociocultural components of gender additionally impact ASCVD risk. Compared with men, women are less likely to seek healthcare that they need. This is particularly true for those with more traditional roles,61 who may prioritize family, household, and caregiver responsibilities over their own health.62 Psychosocial stress is also more evident among women than men, a

reflection of higher prevalence of low education attainment, depression, and anxiety contributing to ASCVD risk.63–65 This is especially the case for women of non-Caucasian ethnicity,66 who are less likely to be aware of ASCVD as a cause of death67 and to seek care.68

Key points

- The impact of several lifestyle-related risk factors is disproportionately greater in women than in men. Adverse changes in weight, lipids, blood pressure, and glucose metabolism with menopause transition highlight potential accelerating cardiovascular risk.
- Female-specific risk factors, such as pregnancy-associated disorders, should be considered to promote earlier ASCVD risk factor assessment.
- Gender-related sociocultural contributors also disproportionately influence cardiovascular health in women.

Does cardiovascular risk prediction differ in women?

As the first manifestation of ASCVD is more likely to be CHD in men but stroke in women,69,70 recent amendments to risk scores in guidelines to include cardiovascular outcomes and fatal and non-fatal events16,71 better reflect the total burden of clinical ASCVD in women. Despite this, current cardiovascular risk prediction models based on traditional risk factors relate to 10-year rather than lifetime risk and are biased by underdiagnosis of events in women thereby underestimating risk.72–76 Even women with a large burden of subclinical atherosclerosis are more likely to be categorized as low risk.77 Given that all prediction models are based on existing data and mostly use retrospective event rates to predict future events, underdiagnosis of events in past studies results in a lower event rate and thus underestimation of risk in models based on these data.72,78

Women generally experience ASCVD events at a later age and have lower event rates than men,79 but given longer life expectancy,80 have a similar lifetime cardiovascular risk.69 Evolution of risk factors over the lifetime also differs between the sexes.81,82 Furthermore, women-specific risk factors are rarely

incorporated when developing cardiovascular risk prediction models, given limited supportive evidence.[83,84] Thus, the concepts of lifetime cardiovascular risk and treatment benefit are promising approaches to tailoring ASCVD prevention in women.[16] Recent findings from the UK Biobank identifying sex differences in genetic loci for CMIT, and correlations with BMI and glucometabolic traits,[85,86] highlight potential for leveraging 'big data' to provide incremental value for ASCVD prediction and prevention in women.

Key points

- Cardiovascular risk prediction based on traditional risk factors over a 10-year span underestimates risk in women.
- Lifetime cardiovascular risk and treatment benefit may be preferable approaches to tailoring cardiovascular disease prevention in women.

Are there sex-related differences in the pathogenesis of atherosclerosis?

A key difference between men and women relates to the levels and ratios of the sex hormones 17β oestradiol, progesterone, and testosterone. Although no randomized controlled trials have unequivocally proved an effect of these sex hormones on ASCVD risk, experimental studies have shown that all three affect biological processes relevant to atherosclerosis.[87] Oestrogens decrease atherosclerotic plaque burden in models of atherosclerosis,[88,89] and oestradiol can increase endothelial nitric oxide production in vitro,[90,91] resulting in increased vasodilation and improved endothelial cell function in mouse models,[92] in isolated human arterioles,[93] and in cis- and transgender human females treated with oestradiol.[94,95] Oestrogens also affect inflammatory pathways, as they can reduce the up-regulation of cytokine-induced E-selectin, vascular cell and intercellular adhesion molecules in endothelial cells,[96] reduce leucocyte recruitment[97] and interleukin-6 expression[98] in (atherosclerotic) mice, and have been shown to prevent vascular smooth muscle cell (SMC) proliferation and extracellular matrix deposition,[99] all key processes that drive atherogenesis.

Oestradiol is also involved in maintaining lipid homeostasis. With lipid loading, oestrogens can modulate reverse cholesterol transport mechanisms, resulting in lower LDL-C and higher high-density lipoprotein cholesterol (HDL-C) levels, and prevent excessive lipid uptake by macrophages.100 However, while oestradiol seems to have favourable effects on many pathogenic mechanisms important in atherosclerosis, the cellular and molecular basis of these phenomena, and the crosstalk of these phenomena are largely unknown.

The experimental data fit well with the observation that after menopause, when oestrogen levels decrease, post-menopausal women show a less-favourable lipid profile than in pre-menopausal women, have less efficient vasodilation, and suppress inflammation less efficiently. This suggests that the increase in ASCVD in post-menopausal women may be caused by more complex mechanisms than just oestrogen depletion, or other unspecified effects of oestrogens on ASCVD. The results of clinical trials of post-menopausal hormone replacement therapy (HRT) are inconclusive for the net effect on primary prevention of ASCVD in post-menopausal women, although systematic review of trials and cohort studies did suggest an increase in stroke risk.101 The Estrogen in Prevention of Atherosclerosis Trial (EPAT) did, however, suggest an oestrogen-dependent reduction in atherosclerosis progression.102

The other main difference between female and male sex are the X and Y chromosomes, which contain many (X) vs. few (Y) genes. An experimental mouse model of atherosclerosis showed that the X-chromosome adversely impacted lipid metabolism, promoting increased absorption and availability of dietary fat, leading to increased atherosclerosis.103 However, human data relating to the impact of the X-chromosome on cardiovascular disease are limited.

Other pathways contribute to differences in ASCVD between women and men. Genome wide association studies identified sex-specific single nucleotide polymorphisms, notably rs16986953 (close to APOB) and rs7865618 (CDKN2B-AS1), associated with cardiovascular disease solely in men.

Integrative systems biology approaches revealed clear differences in gene networks between the sexes.[104,105] Female plaque contained more networks associated with SMC phenotypic modulation and endothelial mesenchymal transition, whereas male plaques exhibited pathways associated with immunoreactivity.[105] Consistent with this, carotid endarterectomy specimens from women showed less inflammatory infiltrates, smaller necrotic cores, and enhanced SMC and collagen content.[106] Imaging studies revealed fewer atherosclerotic plaques with a smaller intima-media thickness and necrotic core, fewer cholesterol crystals, and less calcification, as well as a lower frequency of intraplaque haemorrhage or plaque rupture in women than in men.[106] Thus, despite the paucity of human data, emerging experimental evidence implicates sex as an important player in the pathogenesis of atherosclerosis. Further study is needed to understand mechanisms that drive these differences.

Does sex impact atherothrombosis risk?

Thrombosis often underlies the transformation of a silent atherosclerotic plaque into an acute ischaemic syndrome.[107,108] Over 30 years ago, studies suggested an impaired platelet response to aspirin in women, although conclusive evidence for effects on the underlying processes in thrombus formation is still lacking.[109,110] While there is support for higher platelet activity, platelet counts and on-treatment platelet reactivity and thus greater propensity for thrombosis in women than in men,[111] these differences are small and unlikely to confer a worse clinical prognosis.[112]

It is plausible that female sex hormones (notably oestrogen) regulate procoagulant protein levels, platelet function, and vessel wall biology and composition, which may translate to sex-based differences in thrombosis.[113] Differences in platelet and coagulation activities may, at least partly, explain observations that women are more likely to be aspirin-resistant, to receive distinct benefit from aspirin therapy in primary prevention, and to present with different patterns of venous thrombosis and stroke.[113] Women also have a higher tendency for a hypercoagulable state, although the

underlying mechanism is uncertain. Oestrogen activated platelets and enhanced aggregation and haemostatic activity in a study using platelets showing differential sex-dependent signalling and cellular activation.[114] Another important consideration is bleeding complications, which are more prevalent in women than in men.[111,114,115] Further investigation of sex-based mechanisms regulating thrombosis is merited.

Key points

- Sex (sex hormones and sex chromosomes) influences the pathogenesis of atherothrombosis, but understanding of the underlying mechanisms is limited.
- Sex-based mechanisms may contribute to differing susceptibility to bleeding complications from antiplatelet and anticoagulant therapy in women and men.

Does atherosclerotic cardiovascular disease presentation differ in women?

Ischaemic heart disease

Compared with men, women have smaller coronary arteries with smaller plaques,[116] and a higher burden of microvascular dysfunction with more ischaemia with non-obstructive coronary arteries (INOCA), especially in the 45–65 year age group.[117–119] As symptoms are more diverse and vague than in men, even with obstructive coronary artery disease,[120–122] MI is often silent or missed.[121,123,124]

Women have similar atheroma burden as men,[125] often with concealed atheroma. Both high-risk plaque and non-obstructive left main disease are stronger predictors of major adverse cardiovascular events (MACE) in women than in men, even after adjustment for the presence of stenosis.[126,127] Given the limitations of conventional angiography in women with INOCA,[46] computed tomography angiography is useful to exclude obstructive disease, and to identify plaque burden and low attenuation plaque, a powerful predictor of MI risk.[128,129] Stress positron emission tomography or stress magnetic

resonance imaging can aid diagnosis of coronary microvascular dysfunction. Coronary artery calcium (CAC), although less prevalent in women than men, is associated with a 30% higher risk for cardiovascular death.130 A CAC score >100 or ≥75th age/sex percentile identifies women at elevated risk of MACE; a CAC score >300 was associated with similar event rates as a stable secondary prevention population,131 supporting guideline recommendations for treating a CAC score >300 in primary prevention similar to secondary prevention. Greater lesion size and higher plaque density contribute to higher cardiovascular mortality in women than men with extensive calcified disease.130 Irrespective of the pathophysiology, women with acute coronary syndrome tend to have poorer outcomes than men,132 reflecting increased comorbidities, and delays and underuse of guideline-recommended treatment.133,134

Stroke

Stroke is the third leading cause of death and disability in women.135 Lifetime prevalence is higher and outcome poorer than in men due to older age at onset.136 As for IHD, women with stroke often present with atypical symptoms, increasing the risk of missed or delayed diagnosis.137,138 Unlike men, stroke is more likely to be cardioembolic due to a higher prevalence of atrial fibrillation and less often due to large vessel disease caused by atherosclerosis.136 Some traditional risk factors for stroke such as hypertension, metabolic syndrome, and obesity are more prevalent in women. Other risk factors are only present in women (pre-eclampsia, gestational diabetes, and oral contraceptive use) or increase the risk of stroke more in women than in men (migraine with aura and diabetes).136 Finally, an adverse lipid profile is one of the most important preventable causes of stroke in women.139 Despite evidence that women gain the same benefit as men from statin treatment, they are less likely to be prescribed treatment or attain desired cholesterol levels.6–10,140

Peripheral artery disease

Although peripheral artery disease (PAD) is at least as prevalent in women as in men,[141,142] women are often asymptomatic and therefore less likely to be diagnosed and treated. In the Women's Health and Aging study, only one in six women with PAD were aware of their condition, and two-thirds of those with PAD did not recognize their symptoms.[143,144] Even among symptomatic PAD patients, women are more likely to experience atypical limb symptoms rather than intermittent claudication,[145] with greater and faster reduction in functional status. Consequently, women with PAD are more likely to present with advanced, multilevel lower extremity disease[146–149] and are less likely to be treated effectively with antithrombotic medications, and lipid- and blood pressure-lowering therapy than men with PAD.[150–153] While risk for MACE and mortality is similar,[154,155] women with PAD are at higher risk for above knee amputation than men.[156]

Key points

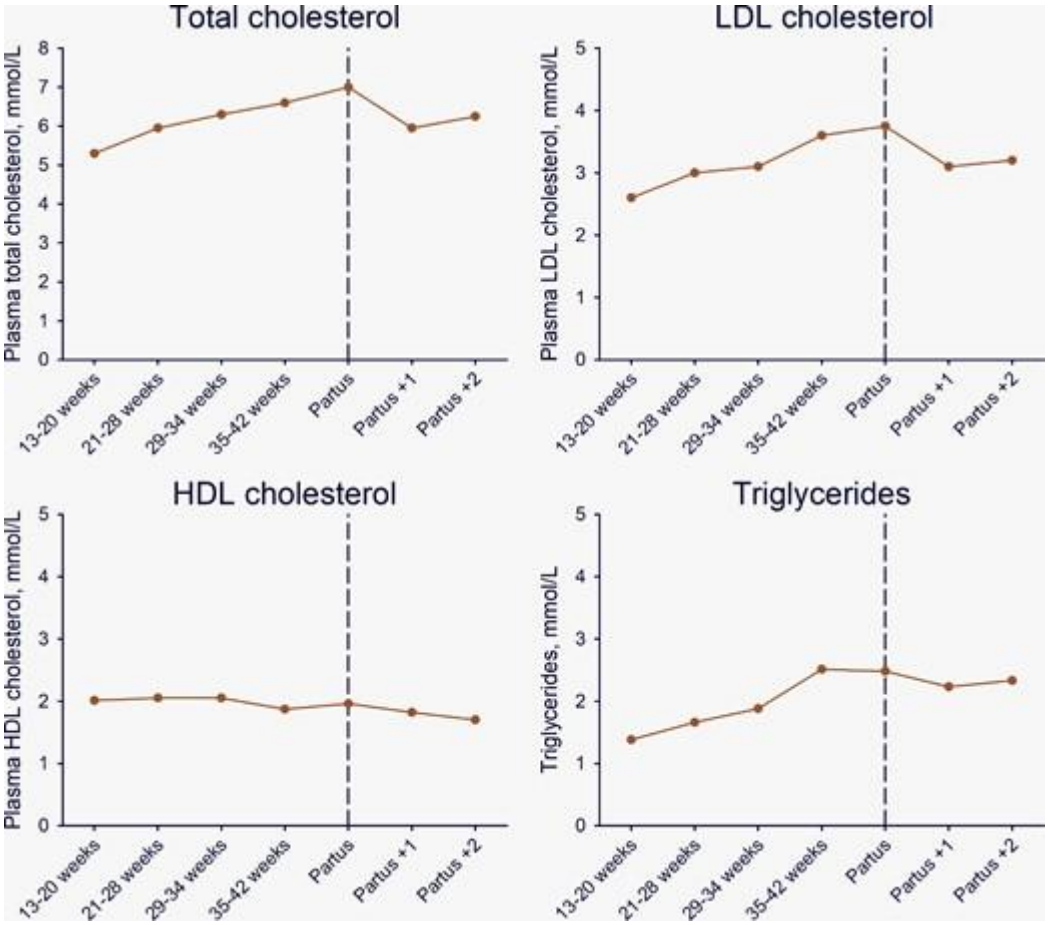
- Symptoms of ASCVD in women are underappreciated and underrecognized.
- Women have a higher burden of microvascular dysfunction than men.
- For all presentations of ASCVD in women, delayed or missed diagnosis is common and contributes to undertreatment.

Cardiovascular risk factors in women: focus on lipids

There is limited information on how female sex influences major lipids, including LDL-C, triglyceride-rich lipoproteins (TRLs), and lipoprotein(a) [Lp(a)]. Cumulative exposure differs (Figure 1), with higher lipid levels from birth in girls than boys,[157–159] persisting during adolescence.[160,161] Lipids also vary during the menstrual cycle (highest at ovulation),[162] a possible consideration in lipid testing. Increases during pregnancy in levels of total cholesterol and LDL-C (~30%) and triglycerides (TGs) (~50% at 35–42 weeks) (Figure 3)[163] are important in women with higher pre-pregnancy levels.[13,14,163] Breastfeeding favourably modulates hyperlipidaemia,[164,165] and when continued for >12 months over the lifetime, is associated with lower risk of ASCVD.[166–168] After

menopause transition, women experience a worsening in the lipid profile (Figure 1) with increases in total cholesterol, LDL-C, and TG levels potentially contributing to accelerating ASCVD risk.169,170

Figure 3



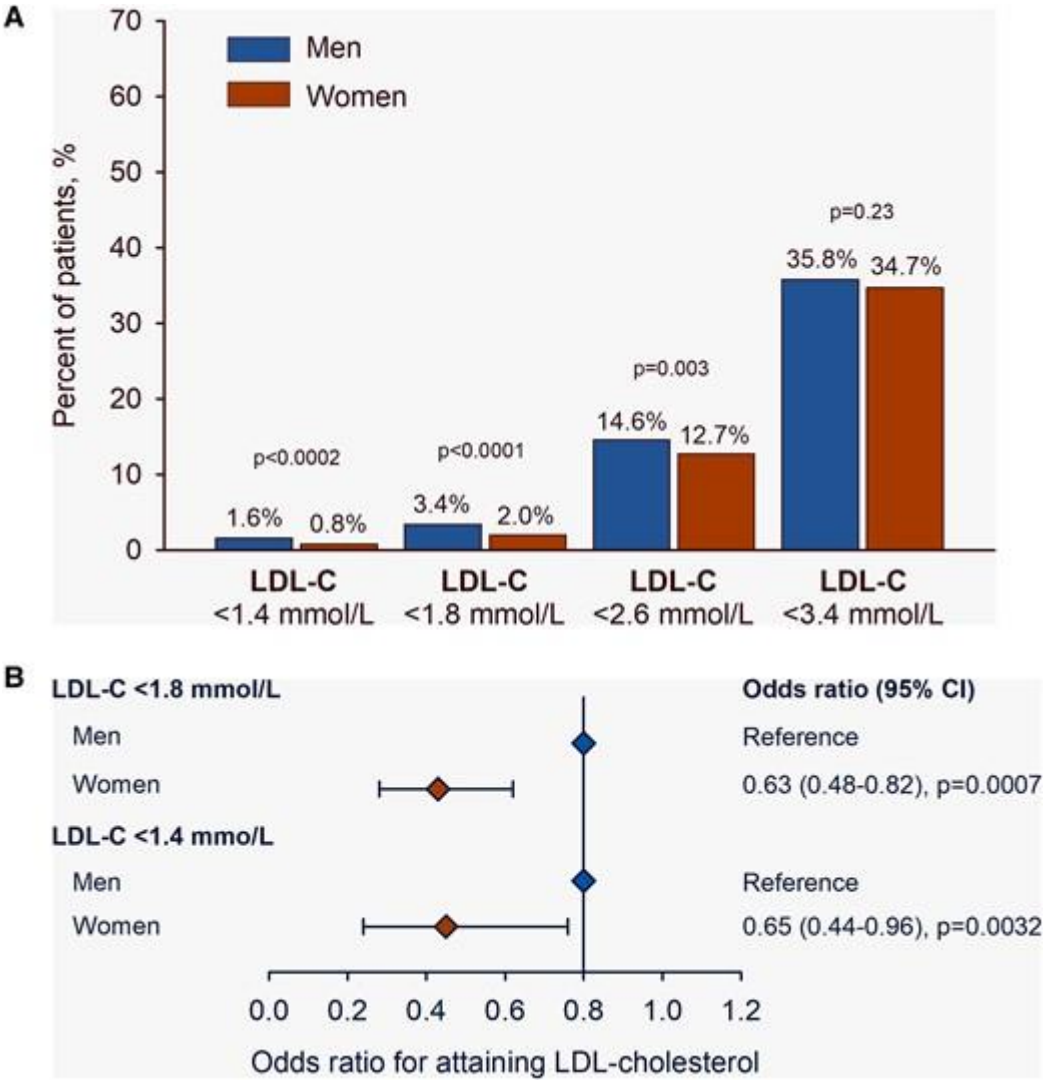
Mean plasma levels of total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol, and triglycerides as a function of pregnancy week, at delivery (partus), and one and two weeks after delivery. Data are medians calculated from the 2.5 and 97.5 percentiles from Klajnbard et al.163 To convert total, LDL, and HDL cholesterol from mmol/L to mg/dL multiply by 38.7. To convert triglycerides from mmol/L to mg/dL multiply by 88.6

Familial hypercholesterolaemia

Familial hypercholesterolaemia is characterized by elevated LDL-C levels compared with the general population.171 Women with FH appear to be at risk of higher cholesterol burden than men with FH for a number of reasons,

including higher LDL-C levels from an early age,172 later diagnosis (on average, by ~2.5 years), and underuse of maximal statin doses or combination LLT.11 Attainment of LDL-C goal is consequently lower (Figure 4), and ~40% of women do not attain levels <1.8 mmol/L (<70 mg/dL) (odds ratio .63, 95% CI .48–.82; P = .0007).11 These disparities in FH care impact ASCVD risk, with registry data showing the highest excess CHD risk among younger women with FH.171,173

Figure 4



Attainment of low-density lipoprotein cholesterol (LDL-C) targets among men and women with familial hypercholesterolaemia on lipid-lowering therapy (statin, ezetimibe, and/or a PCSK9 inhibitor). Panel A shows the percentage of patients on treatment and below different LDL-C thresholds. Panel B shows the

likelihood of attaining an LDL-C below different thresholds according to sex, using men as the reference. The odds ratio was adjusted by age, baseline comorbidities (hypertension, diabetes, smoking, and body mass index), high-density lipoprotein cholesterol, logtriglycerides, lipid-lowering therapy, and index case status. CI, confidence interval. Reproduced with permission11

Adding to this, discontinuation of LLT before and during pregnancy and breastfeeding60 increases LDL-C burden in women with FH. In a recent study of FH subjects with serial lipid measurement over 12 years, a theoretical threshold (area under the curve) for LDL-C burden indicative of higher MI risk (125 mmol/L-years or 5000 mg/dL-years)174 was attained earlier by women than men.12 All FH women had attained this LDL-C threshold by age 33 years, seven years earlier than for FH men.12 Although updated US Food and Drug Administration (FDA) guidance allows for more flexible options for shared decision making in highest-risk women during pregnancy,175 the FDA also acknowledges the lack of data on the efficacy, risks, and benefits of statin therapy during pregnancy and the need for more research, both into safety for the foetus and adverse effect on high-risk women without effective LLT for this time. While limited evidence suggests no higher risk of preterm delivery, low birth weight, or congenital malformation in infants of FH mothers than in the general population with most pregnancies (85%) successfully carried to full-term,176,177 further study is needed. The European Medicines Agency has so far not responded to the statement of the FDA. For now, this panel does not recommend continuing statin therapy during pregnancy and breastfeeding.

Taken together, childbearing (planning, pregnancy, and breastfeeding) represents a considerable loss of LLT (by ~20% at ~30 years) in women with FH.178 This panel stresses the need for close monitoring of FH women during pregnancy and breastfeeding, to minimize their time-off statin therapy. Whether LDL-C goals should be lowered in FH women to compensate for lost treatment merits consideration.

Key points

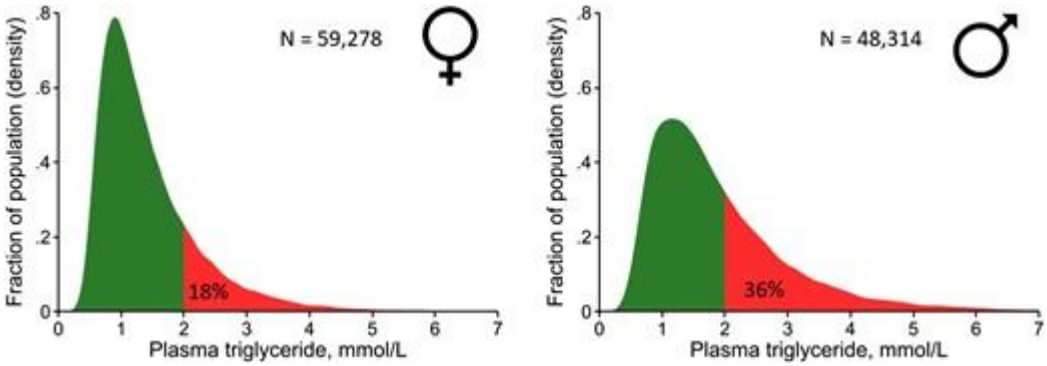
- Female sex influences lipids during transitions (pregnancy, breastfeeding, and menopause). After menopause, women experience a worsening in the lipid profile, potentially contributing to accelerating ASCVD risk.
- The LDL-C burden associated with FH is higher among women than men due to delayed diagnosis, underuse of maximal statin doses with lower LDL-C goal attainment, and discontinuation of statin therapy before and during pregnancy and breastfeeding.
- This panel recommends action to minimize time-off statin therapy for FH women after pregnancy and breastfeeding.

Triglyceride-rich lipoproteins

High levels of plasma TGs are a marker for high levels of TRLs, and as these are metabolized by cells, the cholesterol component—remnant cholesterol or TRL cholesterol—is more important for atherosclerosis.179 High plasma TGs also associate with vascular and systemic inflammation.180,181 Mendelian randomization studies suggested that the observed associations between TGs and remnant cholesterol may be causal182–187; however, with the lack of robust evidence that lowering TGs or remnant cholesterol reduces ASCVD,179,180,188–191 current guidelines do not provide treatment goals.60

As discussed, TGs increase from childhood until ~70 years in women and ~60 years in men (Figure 1).192 From 20–80 years, women consistently have lower TG levels than men, partly explained by higher alcohol intake in men,182 contributing to a lower prevalence with TGs >2 mmol/L (Figure 5). Risk of ASCVD and mortality increases similarly in women and men as TG and remnant cholesterol levels increase.182–184,193

Figure 5



Density distribution of plasma levels of triglycerides in 59,278 women and 48,314 men from the Copenhagen General Population Study. Triglycerides were measured in the non-fasting state and analysed on fresh samples using standard hospital assays. To convert triglycerides from mmol/L to mg/dL multiply by 88.6

Although there is no solid evidence that TG concentration is a better predictor of ASCVD in women than in men, large prospective studies provide insights. The Copenhagen City Heart Study showed a higher risk of MI (HR 1.20, 95% CI 1.05–1.37) and total mortality (HR 1.18, 95% CI 1.10–1.27) in women vs. men per 1 mmol/L increase in non-fasting TG (after multifactorial adjustment for age, total cholesterol, BMI, hypertension, diabetes, smoking, alcohol consumption, physical inactivity, lipid-lowering treatment, post-menopausal status, and HRT).182 A similar trend per 1 mmol/L increase in remnant cholesterol was reported for PAD [HR 1.6, 95% CI 1.3–1.9 in women and 1.2, 95% CI 1.1–1.3 in men (P for interaction sex per remnant cholesterol on risk of PAD = .01)].185 The Emerging Risk Factors Collaboration showed interaction between sex and fasting TG on risk of CHD (P for interaction = .02) with a slightly higher risk per 1 standard deviation (SD) increase in TGs in women (HR 1.06, 95% CI .96–1.16) than men (HR .97, 95% CI .91–1.03) but no interactions between sex and HDL-C or non-HDL-C on risk194. In the Women's Health Study in >28,000 subjects,195 a 1 SD increase in LDL-C was associated with 38% higher CHD risk before age 55 years, but 1 SD increase in non-HDL-C, TGs, and remnant cholesterol increased CHD risk by 67%, 114%, and 66%, respectively. Thus, as for men, elevated TRLs are important to ASCVD risk in women, with lifestyle intervention a priority for management.

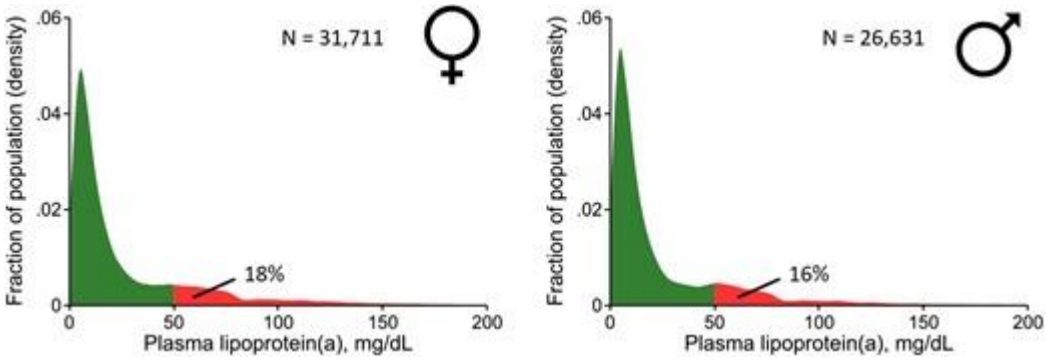
Key points

- Triglyceride levels are a marker for TRL; remnant cholesterol contained in TRL is important for atherosclerosis.
- The association of increasing TG levels and ASCVD risk is similar in men and women.
- While there is currently no solid evidence that TG concentration is a better predictor of ASCVD in women than in men, evidence suggests that TRLs are important risk factors for premature CHD in women.

Lipoprotein(a)

There is clear evidence for the causality of Lp(a) in ASCVD and aortic valve stenosis.196–206 Plasma levels of Lp(a) show similar distribution in men and women, varying with ethnicity207,208 (Figure 6). The Lp(a) concentration increases in women around 50 years coinciding with the onset of menopause209–212 (Figure 1), possibly due to hormonal changes and/or ageing. Indeed, Lp(a) concentration is 12%–20% lower in women on HRT vs. controls,213–215 and approximately doubles in pregnancy.216,217 In the Copenhagen General Population Study in >70,000 individuals, Lp(a) levels were generally similar in men and women aged 20–49 years, but on average 17% higher in women from age 50218(Figure 1). While both sexes show similar associations between high Lp(a) (>40 mg/dL or >83 nmol/L) and cardiovascular morbidity and mortality after age 50 years, higher levels in women (Figure 1) suggest that Lp(a) at this age is a relatively more common cardiovascular risk factor than in men. These findings therefore challenge current recommendations that only one Lp(a) measurement is adequate to capture the lifetime concentration of Lp(a) in women.60,219

Figure 6



Density distribution of plasma levels of lipoprotein(a) [Lp(a)] in 31,711 women and 26,631 men from the Copenhagen General Population Study. The Lp(a) concentration was measured in the non-fasting state and analysed with different assays over time, but all assays were calibrated corresponding to values using the Denka assay on fresh samples. The majority of measurements was performed on fresh samples using this assay. Samples stored prior to measurements were kept at −80°C before measurement. To convert Lp(a) in mg/dL to nmol/L: Lp(a), nmol/L = 2.18 × Lp(a), mg/dL − 3.8332

Key points

- In women, Lp(a) concentration increases during pregnancy, and from the onset of menopause (circa 50 years).
- High Lp(a) levels are more common in women than men after 50 years, which may impact ASCVD risk. This might suggest that guideline recommendations to measure Lp(a) once are inadequate in women.

Call to action for women and atherosclerotic cardiovascular disease

Although ASCVD is the leading cause of death in women, their cardiovascular health is often neglected. Underappreciation of women's ASCVD risk, missed or delayed diagnosis, and undertreatment are important contributors. Despite clear evidence that statin therapy is similarly efficacious in both sexes,220 women at high risk for ASCVD are less likely than men to be prescribed any statin therapy or to receive a statin at guideline-recommended intensity,7 and more likely to refuse or discontinue statin treatment due to perceived side effects.7,221,222 Clearly, action is needed to overcome these inequities.

As discussed in this EAS statement, there are also other important considerations. Women are disproportionately impacted by some lifestyle factors, and sociocultural components related to gender impact risk. Hormonal and chromosomal effects also influence ASCVD progression, although gaps remain in understanding the underlying mechanisms (Graphical abstract). Lipids influence ASCVD risk in women during life course events (pregnancy, breastfeeding, and menopause). During menopause transition, LDL-C levels increase36 and elevated Lp(a) is more common than in men. In women with FH, discontinuation of statin therapy with pregnancy and breastfeeding contributes to greater cumulative cholesterol exposure compared with men with FH.

This panel stresses the importance of early assessment of cardiovascular risk and early treatment of dyslipidaemia in women (Table 2 and Graphical abstract). Further studies to understand the effects of female sex hormones on atherosclerosis development and progression are needed. Targeted action to address these gaps is a priority to reduce the unacceptably high burden of ASCVD in women.

21. Prdm16 mutation determines sex-specific cardiac metabolism and identifies two novel cardiac metabolic regulators

Aims

Mutation of the PRDM16 gene causes human dilated and non-compaction cardiomyopathy. The PRDM16 protein is a transcriptional regulator that affects cardiac development via Tbx5 and Hand1, thus regulating myocardial structure. The biallelic inactivation of Prdm16 induces severe cardiac dysfunction with post-natal lethality and hypertrophy in mice. The early pathological events that occur upon Prdm16 inactivation have not been explored.

Methods and results

This study performed in-depth pathophysiological and molecular analyses of male and female $Prdm16^{csp1/wt}$ mice that carry systemic, monoallelic Prdm16 gene inactivation. We systematically assessed early

molecular changes through transcriptomics, proteomics, and metabolomics. Kinetic modelling of cardiac metabolism was performed in silico with CARDIOKIN. Prdm16$^{csp1/wt}$ mice are viable up to 8 months, develop hypoplastic hearts, and diminished systolic performance that is more pronounced in female mice. Prdm16$^{csp1/wt}$ cardiac tissue of both sexes showed reductions in metabolites associated with amino acid as well as glycerol metabolism, glycolysis, and the tricarboxylic acid cycle. Prdm16$^{csp1/wt}$ cardiac tissue revealed diminished glutathione (GSH) and increased inosine monophosphate (IMP) levels indicating oxidative stress and a dysregulated energetics, respectively. An accumulation of triacylglycerides exclusively in male Prdm16$^{csp1/wt}$ hearts suggests a sex-specific metabolic adaptation. Metabolic modelling using CARDIOKIN identified a reduction in fatty acid utilization in males as well as lower glucose utilization in female Prdm16$^{csp1/wt}$ cardiac tissue. On the level of transcripts and protein expression, Prdm16$^{csp1/wt}$ hearts demonstrate an up-regulation of pyridine nucleotide-disulphide oxidoreductase domain 2 (Pyroxd2) and the transcriptional regulator pre-B-cell leukaemia transcription factor interacting protein 1 (Pbxip1). The strongest concordant transcriptional up-regulation was detected for Prdm16 itself, probably through an autoregulatory mechanism.

Conclusions

Monoallelic, global Prdm16 mutation diminishes cardiac performance in Prdm16$^{csp1/wt}$ mice. Metabolic alterations and transcriptional dysregulation in Prdm16$^{csp1/wt}$ affect cardiac tissue. Female Prdm16$^{csp1/wt}$ mice develop a more pronounced phenotype, indicating sexual dimorphism at this early pathological window. This study suggests that metabolic dysregulation is an early event in the PRDM16 associated cardiac pathology

22. Sex Differences in Thoracic Aortic Disease and Dissection: JACC Review Topic of the Week

Abstract

Despite its higher prevalence among men, women with thoracic aortic aneurysm and dissection (TAAD) have lower rates of treatment and surgical intervention and often have worse outcomes. A growing number of women with TAAD also desire pregnancy, which can be associated with an increased risk of aortic complications. Understanding sex-specific differences in TAAD has the potential to improve care delivery, reduce disparities in treatment, and optimize outcomes for women with TAAD.

Highlights

- Women have a lower prevalence of thoracic aortic disease than mer but often have worse outcomes.
- Substantial inequities exist in the management of patients with thoracic aortic disease based on sex, including surgical interventions.
- Sex-specific thresholds for elective intervention of thoracic aortic disease warrant further exploration.

23. Outcomes of PCSK9 Inhibitors: Does Sex Matter?*

Introduction

Despite significant advancements in medications targeting modifiable risk factors like hyperlipidemia, atherosclerotic cardiovascular disease (ASCVD) remains a significant cause of morbidity and mortality worldwide, affecting both women and men. Lowering low-density lipoprotein cholesterol (LDL-C) levels is a key aspect of ASCVD management. Studies have consistently shown a 22% relative risk reduction of major adverse cardiovascular events (MACE) for every 1 mmol/L reduction in LDL-C levels, whether achieved through statins or other lipid-lowering drugs.[1,2] Recent research has highlighted the potential benefits of achieving even lower LDL-C levels with PCSK9 inhibitors in additional reductions of cardiovascular events.[2,3] Consequently, multiple guidelines now

recommend considering the addition of PCSK9 inhibitors to statin therapy for individuals at high risk of ASCVD.

The clinical approval of PCSK9 inhibitors for both primary and secondary prevention of ASCVD is attributed to their extraordinary efficacy in lowering lipid levels, their cardiovascular benefits, and their excellent safety profile. Through a meta-analysis of randomized trials, a significant reduction of 50 to 60% in plasma LDL-C levels was observed following PCSK9 inhibitors treatment.[4] This reduction was observed even in patients who were already receiving maximally tolerated statin therapy. Furthermore, a Bayesian network meta-analysis indicated that PCSK9 inhibitors may have a potential advantage over statins in terms of preventing MACE.[5]

While there is currently no solid evidence suggesting a significant attenuation of cardiovascular benefits from lipid-lowering therapy and other guideline-directed treatments in women compared to men, it is evident that women often experience disparities in cardiovascular care. Women are more frequently underdiagnosed, undertreated, and receive inadequate follow-up in clinical practice, which can contribute to higher in-hospital mortality rates for acute myocardial infarction among women.[6] In addition to these disparities, women may also face specific cardiovascular risk factors that are unique to their sex. Conditions such as pre-eclampsia, gestational hypertension, premature menopause, polycystic ovarian syndrome, fertility treatments, and autoimmune diseases can significantly increase the risk of future ASCVD in women. Therefore, it becomes crucial to investigate whether PCSK9 inhibitors, a class of drugs with proven efficacy to reduce ASCVD risk, are equally effective in women as they are in men. This investigation holds critical importance as it can guide clinical decisions regarding the prescription of PCSK9 inhibitors in women, ensuring equitable treatment and improved outcomes for female patients.

In this issue of JACC: Advances, Rivera et al[7] conducted a systematic review and meta-analysis to investigate potential sex differences in lipid and cardiovascular outcomes associated with PCSK9 inhibitors. The analysis

included 16 studies with 54,996 patients. It is important to note that only 27.5% of the participants were females, indicating an underrepresentation of women in these trials. Among the studies analyzed, the 2 large cardiovascular outcomes trials, FOURIER and ODYSSEY OUTCOMES, included 27,564 and 18,924 participants, respectively. Both trials had a female percentage of approximately 25%. On the other hand, most of the smaller trials focused on lipid-lowering efficacy and had a higher percentage of women, with more than 40% representation.

In this meta-analysis, the use of PCSK9 inhibitors was associated with a significant reduction in LDL-C levels in both women and men. However, there was a statistically significant difference in the magnitude of LDL-C reduction between sexes. At 12 weeks, PCSK9 inhibitors were associated with a 62.6% reduction in LDL-C in women and a 66.2% reduction in men, with a mean difference of −4.6% ($P < 0.001$). This reduction was slightly attenuated but remained remarkable at 24 weeks, with a 47.5% reduction in women and a 54.1% reduction in men, and a mean difference of −7.1% ($P < 0.001$). These findings align with a sex-specific secondary analysis of the large FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial, which also reported a greater reduction in LDL-C levels in men compared to women at 4 weeks.[8] However, the absolute change instead of percent change in LDL-C levels was reported in the secondary analysis at longer-term follow-up, and thus these data were not included in the present meta-analysis. More importantly, the meta-analysis demonstrated similar effectiveness of PCSK9 inhibitors in preventing MACE in both women and men, with approximately a 15% risk reduction observed in both sexes, and thus supports the use of PCSK9 inhibitors in both sexes.[7]

Interpreting the sex-specific differences related to PCSK9 inhibitors should be considered in the context of findings from other lipid-lowering agents. One collaborative meta-analysis involving 174,000 participants, including 47,000 women, demonstrated that statin therapy effectively reduces LDL-C levels by approximately 30% in both sexes. Additionally, the analysis found that the reduction in MACE per 1 mmol/L reduction in LDL-C was similar between

women and men (16% vs 22% reduction, respectively), after adjusting for detailed cardiovascular risk factors.[9] Similarly, a secondary analysis of the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) trial, which included 18,144 patients with 4,416 women, showed comparable absolute reductions in LDL-C (~16.4 vs 16.7 mg/dL reduction) and similar proportional reductions in MACE (12% vs 5%, respectively, with no significant difference) between women and men.[10] Therefore, a difference of lipid-lowering efficacy between sexes was observed in PCSK9 inhibitors, but not with statins and ezetimibe. This difference could potentially be attributed to variations in plasma PCSK9 levels between sexes. However, comparing outcomes across different classes of lipid-lowering agents can be challenging due to differences in study designs, factors adjusted for in analyses, among other factors.

Commendation should be given to the investigators for conducting a comprehensive and robust analysis of the available evidence on outcomes associated with PCSK9 inhibitors in women and men.[7] However, it is important to consider the potential limitations and exercise caution when interpreting the results. First, the meta-analysis did not account for baseline characteristic differences, other than sex, between women and men in individual trials. Therefore, it cannot conclusively determine the impact of sex on the efficacy and cardiovascular outcomes of PCSK9 inhibitors. The differences in LDL-C reduction observed between women and men could be influenced by non-sex-related differences in baseline characteristics within each group. It is plausible that women and men may have significant disparities in their baseline lipid profiles and cardiovascular risks. Second, the investigators did not evaluate the absolute risk reduction. While the relative risk reduction with PCSK9 inhibitors was similar for both sexes, it remains uncertain whether a comparable absolute risk reduction in MACE would be achieved. This uncertainty also arises from potential differences in baseline cardiovascular risks between women and men.

The ongoing debate regarding the effects of PCSK9 inhibitors between women and men highlights the need for further exploration. To enhance our understanding of sex differences in cardiovascular medicine and improve

clinical decision-making, it is crucial to increase the representation of women in clinical trials and ensure consistent reporting of sex-specific efficacy and safety data, as recommended by the Institute of Medicine report.[11] Collaborative efforts and the utilization of individual participant data from these trials, similar to studies conducted on statins, would be instrumental in elucidating the influence of sex on LDL-C reduction and cardiovascular outcomes associated with PCSK9 inhibitors. Such collaborative initiatives would provide valuable insights into the differential treatment response based on sex, enabling more precise and tailored clinical management specific to each sex.

24. Cardio-Obstetrics Training For CVD Fellowship Programs Focus of JACC Scientific Statement

There is an unmet need for cardio-obstetrics training in cardiovascular disease fellowship programs, and training should be standardized to ensure all fellows in training have the necessary knowledge to treat and refer high-risk cardio-obstetrics patients, according to a JACC Scientific Statement published Oct. 23 in JACC.

Melinda B. Davis, MD, FACC, member of ACC's Reproductive Health and Cardio-Obstetrics Member Section, et al., write that, although maternal mortality rates in the U.S. continue to increase, no standard curriculum for training to ensure a baseline level of knowledge in cardio-obstetrics has been developed. They note that "standards for accredited training in cardio-obstetrics are needed to improve the quality of education and ultimately the quality of care available in this field, and training in cardio-obstetrics should be addressed in the next revision of the Core Cardiovascular Training Statement."

The authors review the core knowledge elements for a cardio-obstetrics training program, which include cardiovascular risk stratification and counseling;

management during pregnancy; planning for labor and delivery; and post-partum follow-up.

The authors propose three levels of training, each including didactics, multidisciplinary patient care and at least one cardio-obstetrics scholarly activity. Level I would provide basic cardio-obstetrics training, as cardiologists across all specialties will need to care for pregnant patients. Level II would provide a higher level of knowledge and competence in cardio-obstetrics to enable cardiologists to provide autonomous focused care for pregnant patients in need of cardiovascular expertise. Level III would prepare cardiologists who intend to lead dedicated cardio-obstetrics programs and/or provide multidisciplinary care to patients at highest risk.

They also make recommendations regarding the assessment of competency, stating the need for "standardized testing of core competencies (Level I) should be included in the American Board of Internal Medicine Cardiovascular Diseases Certification and Recertification examinations."

The authors write, "by standardizing training expectations, the field of cardio-obstetrics will ensure that cardiologists have the skills necessary to care for the growing population of patients with [cardiovascular] in the setting of pregnancy."

25. ACC CardiaCast: Menopausal Hormone Therapy and Hypertension: Newer Data to Help Inform Management of Our Female Patients

Our understanding of menopausal hormone therapy (MHT) and cardiovascular (CV) risk has evolved over the last two decades, with data that can inform decision making. The topic, at the intersection of cardiology and women's health, is an important issue for our female patients and health care providers. Despite this, managing CV risk, and the risk associated with MHT in women, is not emphasized in cardiology training. In this episode, Drs. Abramson, Ahmed, Kalenga, and McLaughlin address these knowledge gaps and discuss new research on the relationship between MHT and hypertension. Additionally, the broader issue of addressing CV risk in post-menopausal women requiring

or requesting MHT and counseling and managing women on hormone therapy from the cardiologist's perspective are also examined.

26. **Reproductive Healthcare Access and the Cardiologist's Role Addressing Hypertensive Disorders of Pregnancy and Cardiovascular Risk**

Introduction

Hypertensive disorders of pregnancy (HDP) prevalence and incidence are increasing in the United States, affecting up to 8% of pregnancies and 15% of birthing individuals.[1,2] HDP carry high maternal morbidity and contribute significantly to maternal mortality.[3] The rise in HDP prevalence is partially due to rising rates of prepregnancy cardiovascular risk factors such as obesity, diabetes, and chronic hypertension. Prevalence of HDP is high in the South and Midwest regions (including Louisiana, Ohio, Missouri, Kentucky, and South Carolina), areas where individuals capable of pregnancy have a higher proportion of prepregnancy cardiovascular risk factors as well.[3-5] There is a dose-effect of prepregnancy cardiovascular risk factors, particularly driven by hypertension and diabetes, such that having >1 risk factor is associated with more adverse maternal and fetal outcomes.[6]

Abernathy et al[7] have now shown that states with restrictive abortion access have a higher proportion of pregnancies with live births complicated by HDP as compared with states with protective abortion access (8.2% in restrictive states vs 6.9% in protective states). Contrary to this, when looking state by state, it should be noted that some of the top 10 states with the highest prevalence of HDP (New Hampshire, Alaska, Oregon, and Vermont), actually have more protective abortion policies and access.[4] In the Abernathy et al[7] study, birthing individuals in restrictive abortion states had a higher proportion of prepregnancy cardiovascular risk factors including obesity, diabetes, and chronic hypertension despite being younger. Although the authors were unable to perform adjusted or causal inference analyses, one could hypothesize that part of the increase in HDP rates in abortion-restrictive states is related to the

higher proportion of prepregnancy cardiovascular risk factors. As referenced in the paper, Medicaid expansion states have been shown to have higher prepregnancy enrollment in Medicaid, better prenatal care, and subsequently more HDP diagnoses. Expansion also correlated with a decline in HDP-associated low birth weight infants.[8] Both higher prepregnancy risk factors and Medicaid expansion could contribute to the noted differences in HDP prevalence by state.

Future studies are needed to assess causal mechanisms for the association between abortion restrictions, prepregnancy cardiovascular risk factors, Medicaid expansion, and HDP. Is it the lack of adequate reproductive health care access in abortion-restrictive states that contributes to disproportionately higher rates of unintended pregnancies in individuals at high-risk for HDP? Or is it that there are more individuals at high-risk for HDP in abortion-restrictive states? Longitudinal studies that compare the effects of changes in abortion policy on HDP prevalence over time may help delineate between these mechanisms. Additionally, studies are needed to investigate the impact of interventions providing more accessible reproductive health care resources on HDP prevalence.

One of the major concerns highlighted by this study is that limiting abortion access to individuals in areas with higher rates of prepregnancy cardiovascular risk factors and higher rates of HDP may have implications for both short- and long-term cardiovascular risk. In addition to the peripartum adverse effects of HDP, recurrent pre-eclampsia has been associated with an increased risk of later life complications including hypertension, ischemic heart disease, and heart failure.[9] As demonstrated by Medicaid expansion, improving abortion and other reproductive health care access may help prevent and identify HDP earlier and thus reduce short-term maternal and fetal complications as well as long-term-associated cardiovascular risk.

As cardiologists, we have a vital role to play in optimizing cardiovascular health and cardiovascular outcomes among reproductive age women and birthing individuals. Cardiologists should incorporate reproductive health in their

approach to prevention of cardiovascular disease. A cardiologist who is well-versed in contraceptive counseling can educate high-risk patients or those on teratogenic medications on the importance of effective contraception.[10] Having streamlined referrals from cardiology to family planning gynecologists can also help patients more easily access needed reproductive care. For birthing individuals, cardiovascular care starts preconception and extends through delivery and into the postpartum period. Furthermore, we should align ourselves with obstetricians and pediatricians to care for postpartum individuals with cardiovascular complications through the vulnerable first year postpartum. This is particularly relevant in abortion-restrictive states.

Individuals in the United States deserve equitable access to reproductive health care that includes abortion access to help prevent adverse maternal outcomes. Cardiologists are well positioned to impact the incidence of HDP and associated adverse cardiovascular outcomes. Care for individuals at risk for HDP should start with involvement of a longitudinal provider in the preconception period and bridge through the postpartum period.

27. Variation in Hypertension in Pregnancy by State Restrictions on Abortion

Introduction

The United States has the highest maternal mortality rate among high-income countries. The rapidly evolving landscape of abortion regulations may worsen this crisis. Recent studies suggest states that restrict abortion have higher maternal mortality rates compared to those with less restrictive regulations.[1] Cardiovascular (CV) conditions are a primary driver of the U.S. maternal health crisis. Chronic hypertension is a critical risk factor for maternal CV complications. Hypertensive disorders of pregnancy (HDP), including gestational hypertension and pre-eclampsia, affect 15% of individuals capable of pregnancy, are leading causes of maternal morbidity, and are associated with a 2-fold higher risk of CV disease in later years.[2] Geographic variation exists in the prevalence of HDP across the United

States.[3] Understanding how CV health of pregnant individuals varies by state abortion policy will contextualize the risk of future CV complications and potential morbidity and mortality related to HDP as abortion is restricted.

We conducted a retrospective cross-sectional study using 2019 U.S. birth certificate data in the Centers for Disease Control and Prevention (CDC) Wide-Ranging Online Data for Epidemiologic Research (WONDER) and Natality Database. U.S. birth certificates include neonatal and maternal demographic, medical, and obstetric data. Birth outcomes associated with hypertensive disorders from U.S. birth certificates have been validated using the CDC WONDER data set[3] We abstracted birth certificate data for patients aged 15 to 45 years with a live birth in 2019. We excluded those with missing data for any primary outcome (chronic hypertension, pre-eclampsia, and eclampsia). In the database, gestational hypertension includes pregnancy-induced hypertension and pre-eclampsia. Consistent with prior research, we relabeled gestational hypertension HDP.[3] We restricted our sample to those with gestational age at delivery between 24 and 42 weeks. Eclampsia was not reported in South Carolina and Tennessee, thus is not reported here.

States were grouped into 3 categories using the Guttmacher Institute database on state policy environment on abortion as of October 16, 2022.[4]

We characterized the prevalence of chronic hypertension and HDP among birthing people in states restrictive, intermediate, or protective of abortion. We compared demographic and clinical characteristics across state abortion regulations. We used census data to examine state level deprivation including proportion of uninsured, living in poverty as defined by the American Census Bureau based on the size of a family and weighted average income thresholds, and multidimensional deprivation index.[5] We used chi-squared tests to compare variables between states restrictive, intermediate, and protective of abortion. Values that were unknown, not stated, or not reported were not included in statistical testing. Analysis was complete using R version 4.2.2. This study was deemed exempt by the University of Pennsylvania Institutional Review Board.

A total of 3,676,932 births in 2019 were included in the analysis. There were 26 states categorized as restrictive, 11 intermediate, and 13 protective of abortion. We noted significant differences in health indicators of birthing people in states restrictive of abortion compared to protective of abortion (**Figure 1A**). Birthing people in restrictive states were more often younger, less educated, insured by Medicaid, had elevated body mass index, tobacco users, and experience late entry to prenatal care, short interpregnancy interval, and preterm birth compared to those in protective states. Also, the uninsured population, official poverty measure, and deprivation index were greater in restrictive states.

We found significant differences in hypertension diagnoses, at the state level, according to state abortion regulations (**Figure 1B**). In states restrictive of abortion, 2.4% of births occurred in patients with chronic hypertension compared to 2.1% in intermediate and 1.9% in protective states ($P < 0.001$ across the 3 groups). The same trend persisted for HDP, which affected 8.2% of all births in restrictive states, 8.0% of births in intermediate states, and 6.9% of births in protective states ($P < 0.001$ across the 3 groups). Prevalence of eclampsia also showed significant variation.

The burden of hypertensive disorders among birthing people varies in tandem with state abortion regulations. States with restrictive abortion policies have the highest prevalence of chronic hypertension, HDP, and eclampsia. These findings may be explained in part by differences in patient characteristics and social determinants of health. A limitation of this study is the use of aggregate data reported at the state level, thus precluding control for these confounders and any causal inference conclusions. As a result, our analysis is descriptive and demonstrates that significant variation in HDP exists across states by abortion policy.

This finding is relevant as the projected increase in birth rates as a result of restrictive abortion legislation may increase the number of individuals entering pregnancy with CV risk factors and who experience pre-eclampsia and other CV complications in pregnancy. As the number of pregnant people with CV

complications of pregnancy rise, so too does health services utilization and medical expenditures related to their care, losses related to future productivity, and the immeasurable cost incurred by those unable to access abortion when desired. Health systems and policy makers should be aware of the growing need to adopt and implement evidence-based strategies to curb the contribution of hypertension in pregnancy to prevent worsening maternal outcomes and, subsequently, long-term CV health of individuals with pregnancy complications

28. Sex Differences in Cardiovascular Outcomes and Cholesterol-Lowering Efficacy of PCSK9 Inhibitors: Systematic Review and Meta-Analysis

Background

Guideline-recommended low-density lipoprotein cholesterol (LDL-C) thresholds are often not achieved in women. The proprotein convertase subtilisin/kexin type-9 inhibitor (PCSK9i) monoclonal antibodies can help further reduce LDL-C and major adverse cardiovascular events (MACE) although differences in efficacy by sex and type are less understood.

Objectives

The authors sought to determine if there are differences in the efficacy of LDL-C lowering and reduction in the risk of MACE by sex and type of PCSK9i.

Methods

A comprehensive literature search was done through October 17, 2022, for published trials comparing PCSK9i vs control. Outcomes assessed were LDL-C reduction and incidence of MACE following the use of PCSK9i vs placebo, stratified by sex and type of PCSK9i used.

Results

We identified 16 trials with 54,996 adults, and 15,143 (27.5%) of them were female. PCSK9i significantly reduced MACE compared to placebo in both women (HR: 0.86, 95% CI: 0.74-0.97, P < 0.001) and men (HR: 0.85, 95% CI: 0.79-0.91, P < 0.001) with no significant sex difference (MD −0.01, 95% CI:

−0.14 to −0.13, P = 0.930). PCSK9i also significantly reduced LDL-C levels in both sexes at 12 weeks (females: MD −62.57, 95% CI: −70.24 to −54.91, P < 0.001; males: MD −66.19, 95% CI: −72.03 to −60.34, P < 0.001) and 24 weeks (females: MD −47.52, 95% CI: −52.94 to −42.09, P < 0.001; males: MD −54.07, 95% CI: −59.46 to −48.68, P < 0.001). Significant sex difference was seen in the LDL reduction of PCSK9i for both 12 weeks (males vs females: MD −4.55, 95% CI: −7.34 to −1.75, P < 0.01) and 24 weeks (males vs females: MD −7.11, 95% CI: −9.99 to −4.23, P < 0.001).

Conclusions

The use of PCSK9i results in significant LDL-C and MACE reduction in both males and females. While there is no significant sex difference in MACE reduction, LDL-C reduction is greater in males than in females. Our data support the equal use of PCSK9i in all eligible patients, regardless of sex.

29. Sex-biased TGFβ signalling in pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a rare cardiovascular disorder leading to pulmonary hypertension and, often fatal, right heart failure. Sex differences in PAH are evident, which primarily presents with a female predominance and increased male severity. Disturbed signalling of the transforming growth factor-β (TGFβ) family and gene mutations in the bone morphogenetic protein receptor 2 (BMPR2) are risk factors for PAH development, but how sex-specific cues affect the TGFβ family signalling in PAH remains poorly understood. In this review, we aim to explore the sex bias in PAH by examining sex differences in the TGFβ signalling family through mechanistical and translational evidence. Sex hormones including oestrogens, progestogens, and androgens, can determine the expression of receptors (including BMPR2), ligands, and soluble antagonists within the TGFβ family in a tissue-specific manner. Furthermore, sex-related genetic processes, i.e. Y-chromosome expression and X-chromosome inactivation, can influence the TGFβ signalling family at multiple levels. Given the clinical and mechanistical similarities, we expect that the conclusions arising from this review may apply also to hereditary haemorrhagic

telangiectasia (HHT), a rare vascular disorder affecting the TGFβ signalling family pathway. In summary, we anticipate that investigating the TGFβ signalling family in a sex-specific manner will contribute to further understand the underlying processes leading to PAH and likely HHT.