

News in February 2023

1. Risk and Trajectory of Premature CVD in Women With a History of Pre-Eclampsia

The American College of Cardiology/American Heart Association 2018 Guideline on the Management of Blood Cholesterol lists pre-eclampsia as a risk-enhancing factor for physician–patient risk discussion for cholesterol management. The current study of premature ischemic cardiovascular disease in women with a history of pre-eclampsia escalates the concern of the adverse predictive impact of pre-eclampsia on premature ischemic cardiovascular disease. This register-based study from Denmark included over one million women with at least one pregnancy between 1978 and 2017 and examined the cumulative indices of acute myocardial infarction and ischemic stroke. Up to 2% of women with pre-eclampsia in a first pregnancy incur acute myocardial infarction or stroke within 2 decades of delivery. After delivery, women with pre-eclampsia had threefold and fourfold higher rates of myocardial infarction and stroke, respectively. Women with pre-eclampsia aged 30 to 39 years had fivefold and threefold higher rates of acute myocardial infarction and stroke, respectively, than women of comparable age without pre-eclampsia. The authors suggest that pre-eclampsia history can be useful in identifying women at increased risk of cardiovascular disease and that targeted interventions should be initiated soon after delivery.

Pre-eclampsia in the US is a major cause of maternal and perinatal morbidity and mortality; it occurs in up to 10% of pregnancies. Pre-eclampsia has increased by about 25% in the past 2 decades, disproportionately affecting African American women, and is more prevalent both at the extremes of reproductive age and with underlying cardiovascular risk factors. The US Preventive Services Task Force recommends screening for pre-eclampsia by blood pressure measurement at each pregnancy visit. In addition, the US Preventive Services Task Force recommends the use of low-dose aspirin (81

mg/day) as preventive medication after 12 weeks of gestation in women at high risk for pre-eclampsia.¹

The Chronic Hypertension and Pregnancy trial demonstrated that a treatment strategy targeting a blood pressure of less than 140/90 mm Hg for pregnant women with chronic hypertension improved outcomes compared with a regimen that initiated treatment only for blood pressure at or above 160/105 mm Hg.² Whether this regimen will decrease the occurrence of pre-eclampsia is unknown, but it offers promise of benefit for women who have hypertensive disorders of pregnancy.

Recommendations after pre-eclampsia include extended lactation (which decreases the risk of maternal hypertension), achieving an optimal BMI, smoking cessation, a healthy diet, regular exercise, and planned long-term surveillance.

A further concern is identified in a cohort study involving almost 8.5 million participants in Nordic countries which identified that offspring exposed to maternal pre-eclampsia had a 33% increased risk of ischemic heart disease and a 34% increased risk of stroke in childhood and young adulthood and that the associated risk of stroke was higher with severe forms of pre-eclampsia.³

2. AMI, Stroke Risk Elevated for Women With Preeclampsia Within 20 Years

Women with a history of preeclampsia have a significantly increased risk for acute myocardial infarction (AMI) and ischemic stroke within and after 10 years of delivery, according to a study published online Jan. 26 in the *European Journal of Preventive Cardiology*.

Sara Hallum, from the University of Copenhagen in Denmark, and colleagues conducted a register-based study including 1,157,666 women with more than one pregnancy between 1978 and 2017. The cumulative incidences and hazard ratios for AMI and ischemic stroke were estimated.

The researchers found that up to 2 and 1.2 percent of women with preeclampsia in their first pregnancy and preeclampsia-free women, respectively, had an AMI or stroke within two decades of delivery; the differences in cumulative incidence were seen up to seven years after delivery. Women with preeclampsia had significantly elevated rates of AMI and stroke 10 years after delivery compared with women without preeclampsia (hazard ratios, 4.16 and 2.59); more than 20 years later, rates remained doubled. For women aged 30 to 39 years, those with preeclampsia had higher rates of AMI and stroke compared with those without preeclampsia (hazard ratios, 4.88 and 2.56, respectively).

"Our findings suggest that a history of preeclampsia should focus attention on a group of women at potentially high risk of CVD [cardiovascular disease], with the aim of improving risk assessment and disease prevention in this vulnerable group," the authors write.

3. ASA: Sex Differences Seen in Use of Dual Antiplatelet Therapy After Minor Stroke

Dual antiplatelet therapy (DAPT) is underused following transient ischemic attack (TIA) and minor acute ischemic stroke (AIS), particularly in women, according to a study presented at the annual American Stroke Association International Stroke Conference, held from Feb. 8 to 10 in Dallas.

Jonathan Solomonow, M.D., from the University of Maryland Medical Center in Baltimore, and colleagues examined variations in single versus dual antiplatelet prescribing practices at the time of discharge within the University of Maryland Stroke Clinical Network consisting of nine stroke centers located in rural, suburban, and urban hospitals. The analysis included 2,953 adults with a TIA or a minor AIS (admission National Institutes of Health Stroke Scale score <5), who were admitted to the network from 2018 through 2021.

The researchers found that DAPT was prescribed at the time of discharge to 40 percent of patients overall. However, gender was a significant factor, with men

more likely to get prescribed DAPT than women (43 versus 37 percent). Body mass index (BMI) did not have a lone effect on number of antiplatelets prescribed, but when it was included as a covariate, there was a significant effect seen on the number of antiplatelets prescribed. Higher BMI was associated with a lower likelihood of receiving DAPT. Differences were not significant for age, race, or whether or not the patient was discharged from a tertiary center.

"All stroke survivors, regardless of sex, should receive optimal proven medications for stroke prevention, including DAPT when medically appropriate," Solomonow said in a statement. "Identifying systemic inequities is essential to improving patient care across all demographics."

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5. Maternal CV Risk After Adverse Pregnancy Outcome Can Last Over 40 Years

Approximately 30% of women have a major pregnancy complication such as preterm delivery, preeclampsia, or gestational diabetes in their reproductive years, which may confer elevated risk for ischemic heart disease that persists for decades, a Swedish national cohort study shows.

Despite the known association of some adverse pregnancy outcomes with higher future maternal risk of ischemic heart disease or traditional CV risk factors, these patients often slip through the cracks, with the long-term risks of pregnancy complications often unmentioned between women and their physicians in routine practice, noted lead author Casey Crump, MD, PhD (Icahn School of Medicine at Mount Sinai, New York, NY).

“The important thing is to recognize that all of these major adverse pregnancy outcomes are important lifelong risk factors for ischemic heart disease,” he said. “These should be considered when evaluating cardiovascular risk because it's an opportunity to identify high-risk women much earlier than with traditional risk factors alone.”

Crump and colleagues' study of over 2 million women in Sweden, which was published in the *BMJ*, found that those with one or more adverse pregnancy outcomes had increased risk for CAD out to 46 years, with those who experienced multiple adverse pregnancy outcomes and combinations of certain adverse events having even greater increased risk.

Commenting on the study for TCTMD, Michael C. Honigberg, MD (Massachusetts General Hospital and Harvard Medical School, Boston, MA), said while the reasons behind the association aren't entirely clear, he believes they reflect shared upstream risk factors.

“Others have speculated that there might be a causal effect of the adverse pregnancy outcome itself on future risk of cardiovascular disease, and it's possible that there is a bidirectional relationship, although how a pregnancy outcome could continue to impart enduring risk 46 years later seems a little bit hard to explain biologically,” Honigberg noted. “So, I think what these associations are actually showing us is that women who experience some of these adverse pregnancy outcomes have inherent genetic or other environmental risk factors that aren't fully captured by conventional cardiovascular disease risk factors.”

Some Risk Interactions Seen

For the study, Crump and colleagues examined data on 2,195,266 Swedish women (median age 27 years at first delivery) who gave birth between 1973 and 2015.

While some prior studies have looked at the effect of individual adverse pregnancy outcomes on later CV risk, Crump and colleagues looked at five major types: preterm delivery (< 37 weeks gestation), small for gestational age, preeclampsia, other hypertensive disorders of pregnancy, and gestational diabetes.

Among the 30% of women who experienced at least one of the five complications, delivery of a small-for-gestational-age infant was the most common, followed by preterm delivery. Similarly, of the more than 8% of women who had two or more of the five complications, the most common combination was preterm delivery and delivery of a small-for-gestational-age infant.

Over the follow-up period (median 25 years, maximum 46 years), 3.8% of women were diagnosed with ischemic heart disease. The median age at diagnosis was 58 years.

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After adjustment for other adverse pregnancy outcomes and maternal factors, those who had hypertensive disorders of pregnancy had the greatest risk of a CAD diagnosis in the 10 years after pregnancy (HR 2.09; 95% CI 1.77-2.46), followed by those with preterm delivery (HR 1.72; 95% CI 1.55-1.90), preeclampsia (HR 1.54; 95% CI 1.37-1.72), gestational diabetes (HR 1.30; 95% CI 1.09-1.56), and a small-for-gestational-age infant (HR 1.10; 95% CI 1.00-1.21).

Looking further out from the pregnancy, having a small-for-gestational-age infant was associated with the highest risk of CAD at 10 to 19 years postpartum, and gestational diabetes was associated with the highest risk at 20 to 29 years. For women with longer follow-up, adjusted hazard ratios for CAD decreased but remained elevated compare with those without adverse pregnancy outcomes in the 30- to 46-year follow-up window.

The researchers also looked at interactions between adverse event types, finding that preterm delivery had positive additive interactions with preeclampsia, other hypertensive disorders of pregnancy, and gestational diabetes on CAD diagnosis. Additionally, preeclampsia accounted for significantly more CAD diagnoses in women who also had gestational diabetes, and vice versa.

Crump and colleagues also attempted to adjust for background risk by performing a co-sibling analysis, which found that most of the associations persisted after controlling for shared familial genetic and other environmental factors, although they acknowledge that these types of analyses “do not fully capture genetic risk, and it is possible that underlying genetic pathways may partly explain future risks of adverse pregnancy outcomes and ischemic heart disease or its precursors.”

Increased Awareness Needed

Crump told TCTMD that while the American Heart Association now recommends asking about pregnancy history when evaluating cardiovascular risk in women, “we know that's not consistently done in clinical practice, especially in primary care settings where most women receive their care.” He added that the exciting thing about the new findings “is it provides an opportunity to identify high-risk women potentially much earlier in their life, and then start preventive actions much earlier to hopefully improve their long-term outcomes.”

Even as someone who does research in this space, Honigberg said he recognized that he wasn't always capturing reproductive history in his own patients, so he added it to his clinical templates as a prompt. Still, he said it's unclear to many clinicians what they're supposed to do with this information.

“We need clear guidelines, clearer recommendations about how folks can incorporate this history in their clinical care, because if we had that, then [physicians] would be much more likely to ask about it,” he said.

Honigberg added that another glaring issue is that overt CVD risk factors are routinely ignored in younger people, including those who have just given birth and are otherwise healthy.

“The default is to say this is a young person who's at low short-term risk, so we don't have to be quite as aggressive about treating early or subclinical risk factors, and I think that's the wrong approach,” he explained. “We also now have mounting data . . . highlighting that the population with adverse pregnancy outcomes develops subclinical atherosclerosis detectable by CT imaging earlier than women with normotensive or uncomplicated pregnancies.”

Honigberg said those women may represent a prime population to employ early coronary artery calcium testing to look for premature development of subclinical atherosclerosis and begin early initiation of preventive therapies like statins.

Finally, a remaining issue that needs to be addressed is best practices for intervening soon after pregnancy for women who have had an adverse pregnancy outcome, knowing that it is a time of increased stress and too little self-care.

“We need to be thinking a little bit creatively about how care delivery systems can be optimized for when women are most receptive and able to incorporate education and lifestyle modification into their lives,” he added.

6. Association of reproductive factors with cardiovascular disease risk in pre-menopausal women: nationwide population-based cohort study

Background

Although the morbidity and mortality of cardiovascular diseases (CVD) are rising in young women, the risk factors of CVD among Korean pre-menopausal women have not been intensively investigated.

Aims

To determine how age at menarche and other female reproductive factors are associated with the risk of CVD in pre-menopausal women.

Methods and results

A total of 1 088 992 pre-menopausal women who participated in health screening in 2009 were included. The study outcomes were myocardial infarction (MI) and ischaemic stroke. Cox proportional hazards regression analysis was conducted with adjustment of traditional CVD risk factors and reproductive factors.

Results

Mean age was 43.8 ± 5.3 years (98.9%, < 55 years), 3.5% were current smokers, and 1.2% were heavy drinkers. During a mean follow-up of 8.3years [9 032 685.9 person-years (PY)], there were 10 876 CVD events (1.0 per 1000 PY).With later menarche, the risk of CVD increased; ≤ 12 years [adjusted hazard ratio (HR) 1.04, 95% confidence interval 0.93–1.16], 13 years (reference), 14 years (1.06, 0.98–1.14), 15 years (1.15, 1.07–1.24), 16 years (1.23, 1.14–1.34), and ≥ 17 years (1.33, 1.24–1.44). Compared with non-users, oral contraceptives (OC) users (≥ 1 year) had an increased risk of CVD (1.11, 1.01–1.22) (P for trend = 0.007).

Conclusions

Later menarche than the mean age at menarche (13 years old) and the use of OC (≥ 1 year) were associated with a higher risk of CVD, after adjusting for traditional cardiovascular risk factors. This study suggests that female reproductive factors could be unique risk factors for CVD in pre-menopausal women.

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8. Gender and Racial Disparities in Provision of Medications and Lifestyle Counseling in Ambulatory Settings for ASCVD

IMPORTANCE

Atherosclerotic cardiovascular disease (ASCVD) continues to be highly prevalent in the US. The 2013 American College of Cardiology and American Heart Association (ACC/AHA) treatment guidelines reevaluated evidence-based practices for reduction of ASCVD in men and women from high-quality randomized trials and meta-analyses recommending the use of statin therapy,

aspirin prescription, and lifestyle counseling for adults with ASCVD. Population trends in secondary prevention strategies for patients with ASCVD among primary care settings is currently lacking, limiting ability to evaluate impact of guideline implementation.

OBJECTIVE

To examine temporal and sociodemographic trends in secondary prevention strategies in patients with ASCVD between 2006 and 2016 in a nationally representative, ambulatory care database.

DESIGN, SETTING, AND PARTICIPANTS

This cross-sectional study analyzed data from the National Ambulatory Medical Care Survey (NAMCS), which is an annual survey conducted to represent the national US population and contains information on ambulatory office-based patient visits, including medical conditions, services provided, and demographic characteristics. Participants were adults aged 21 years and older with prevalent ASCVD identified via International Classification of Disease codes between 2006 and 2016. Data were extracted and analyzed in March 2021.

MAIN OUTCOMES AND MEASURES

Data were separated by calendar year pre-2013 (2006 to 2013) and post-2013 (2014 to 2016). Outcomes included statin therapy, aspirin prescription, and lifestyle counseling (eg, nutrition, exercise, weight reduction) service provided at clinic visits.

RESULTS

There were 11 033 visits for adults with ASCVD, representing a weighted total of 275.3 million visits nationwide; 40.7% (112.1 million [weighted]) were women, 9.2% (25.4 million [weighted]) were Hispanic, 9.9% (19.0 million [weighted]) were non-Hispanic Black, 90.1% (172.7 million [weighted]) were non-Hispanic White, and 40.6% (112.1 million [weighted]) were from cardiology clinics. Of 11 033

patient visits, 5507 patients (49.9%) were prescribed statin therapy, 5165 patients (46.8%) were using aspirin, 2233 patients (20.2%) received lifestyle counseling. Statin therapy increased from 9.3 million individuals (45.3%) in 2006 to 14.9 million individuals (46.5%) in 2016, and aspirin prescriptions increased from 8.5 million individuals (41.3%) in 2006 to 15.2 individuals (47.5%) in 2016. Women were less likely than men to receive medications for secondary prevention: among women, 48.8 million (43.3%) received statins (vs 85.9 million men [52.7%]), 44.7 million (39.8%) received aspirin (vs 79.1 million men [48.5%]), and 25.7 million (22.9%) received lifestyle counseling services (vs 37.5 million men [23.0%]).

CONCLUSIONS AND RELEVANCE

These findings suggest only modest increases in statin and aspirin prescription since 2006; however, lifestyle counseling use decreased in recent years. Women and Black patients continued to be less likely to receive secondary prevention ASCVD treatment. Adherence to guideline-directed secondary prevention recommendations remained low (less than 50%) in patients with ASCVD, especially with regards to lifestyle counseling, suggesting the need for more implementation research.

9. Understanding Sex Differences in Acute and Chronic Coronary Syndromes

Sex differences in the presentation and outcomes of coronary artery disease (CAD) have been well documented in previously published studies.¹⁻³ Women have a higher rate of adverse events after a myocardial infarction (MI) as compared with men, despite a lower angiographic disease burden.^{4,5} Although women are more likely to have comorbidities, including diabetes and hypertension, angiographically, they are less likely to have obstructive CAD as compared with men.¹ Because the uptake of intracoronary imaging has been low, understanding has been challenging.

Sex differences in atherosclerotic plaque burden, volume, and consistency, as well as endothelial dysfunction, have been reported from largely observational studies, both in chronic as well acute coronary syndrome (ACS) settings.^{5,6} However, whether the absolute burden of atherosclerotic plaque in women differs from men remains uncertain. This is particularly important, as an acute coronary event is determined by the characteristics of the atherosclerotic plaque, not by luminal diameter stenosis.^{7,8}

The role of intravascular imaging in the assessment of atheroma burden in early coronary atherosclerosis, chronic coronary syndrome (CCS), and ACS is well established. Currently, the major intracoronary imaging technologies include cardiac CT (CCT), intravascular ultrasound (IVUS), optical coherence tomography (OCT), and near-infrared spectroscopy (NIRS). Pathophysiologically, progressive evolution of atherosclerotic plaque comprises sequentially of pathologic intimal thickening, fibrotic plaque, lipidic plaque, fibroatheroma, thin-cap fibroatheroma (TCFA), and fibrocalcific plaque.⁹

Among the intravascular imaging modalities, IVUS in particular—because of its precise assessment of atheroma burden—has enhanced our understanding of this natural history of atherosclerosis, as well as its response to risk-factor-modifying medical therapies.¹⁰ Due to difficulties in randomizing patients in imaging trials, and due to the underrepresentation of women in coronary trials overall, data on sex differences in plaque morphology are largely pooled from observational studies and predominantly limited to IVUS and OCT.¹ This article provides an overview of these sex differences on intravascular imaging pertaining to CCS and ACS ([Figure 1](#)).

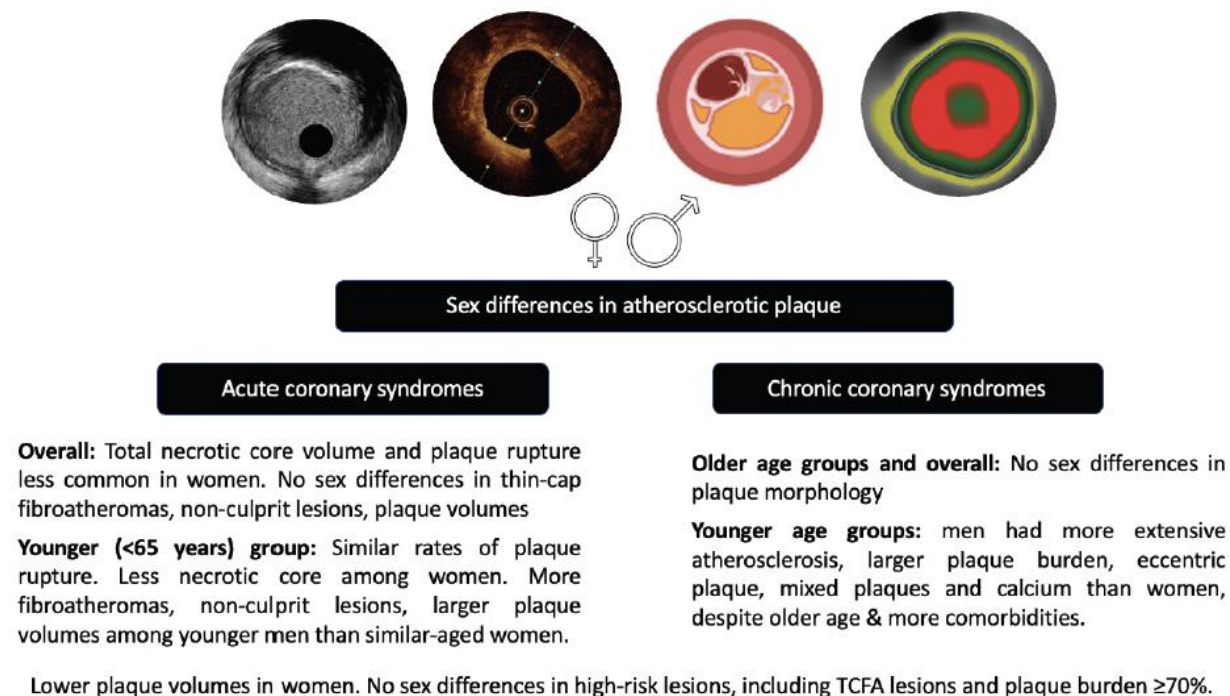


Figure 1. Sex differences in atherosclerotic plaque on intravascular imaging.

SEX DIFFERENCES IN PLAQUE VOLUME IN CCS

In a multimodality intravascular imaging study of 383 patients with stable CAD, Bharadwaj et al reported no sex differences in plaque morphology on OCT (including maximum lipid arc, lipid volume index, lipid length, TCFA incidence, and calcification). Similarly, sex was not an independent predictor of severe plaque burden by IVUS; there were no sex differences in plaque characteristics, except for an increase in the reference segment plaque burden in men. No difference in maximal lipid core burden index (LCBI) at the 4-mm maximal segment was noted on NIRS. Although women were older (66 ± 10 vs 62 ± 11 years) and had more comorbidities in this study, the totality of evidence generated suggests sex is not a determinant irrespective of the imaging modalities employed.¹¹

Similarly, in a study by Kornowski et al of 169 women and 549 men with stable angina, no sex differences (quantitative or qualitative) in coronary atherosclerotic

plaques could be identified on preinterventional IVUS; similar reference and lesion plaque burden, calcium, and eccentricity were seen for women and men.¹²

Nicholls et al undertook a sex-based serial IVUS comparison of extent of baseline coronary atheroma and its subsequent change in response to established medical therapies.¹⁰ Among the 978 participants, despite women being older and having more comorbidities (including diabetes, hypertension, total and low-density lipoprotein cholesterol), women had less atheromatous plaque, as reflected by a lower percent atheroma volume and total atheroma volume, both of which remained lower even after multivariate adjustment. Women also had smaller vessels and lumen volume, but there were no sex differences in arterial remodeling at lesions with the largest plaque burden. Notably, the median age of women and men in this study was 57 and 56 years, respectively, which is lower than other studies and may be a significant point given interactions of age with plaque characteristics in some studies.¹⁰

A smaller study (N = 93) in which plaque morphology was compared by both CCT and virtual histology (VH) IVUS, more extensive atherosclerosis in the form of larger plaque burden and more mixed plaques as well as larger arcs of calcium were seen in men than women, predominantly among those aged < 65 years, with no such differences in plaque patterns among those aged ≥ 65 years. On VH IVUS, TCFA prevalence was also higher among men aged < 65 years compared with women in that age group.¹³

Another study of simultaneous assessment of IVUS and endothelial function in 142 patients with early CAD also demonstrated a greater atheroma burden in the left main and proximal left anterior descending (LAD) artery, more eccentric atheroma, and more diffuse endothelial dysfunction in men compared with women. Sex was an independent predictor of atheroma burden in both the left main and proximal LAD arteries by multivariate analysis. This study, which enrolled a relatively younger population (mean age, 49.3 ± 11.7 years), and wherein male sex was an independent predictor of atheroma burden, is

somewhat limited by its observational nature, referral bias, and nonuniformity of atheroma extent in the coronaries.⁵

SEX DIFFERENCES IN PLAQUE VOLUME IN ACS

Among ACS patients, the PROSPECT trial assessed plaque characteristics of both culprit and nonculprit lesions (NCLs) by multimodality imaging, including angiography, grayscale IVUS, and VH IVUS. In the PROSPECT sex-based analysis, although there were no sex differences angiographically in the overall number of culprit lesions, women had fewer NCLs and fewer vessels with NCLs compared with men. On IVUS too, although women had fewer NCLs, there were no sex differences in plaque burden per lesion (55.6% vs 55.3%; $P = .35$) and female sex was not a predictor of severe ($> 70\%$) plaque burden. However, although women were less prone to plaque rupture (6.6% vs 16.3%) and had less total necrotic core volume than men, no sex differences were seen for other plaque phenotypes, including TCFA, thick-cap fibroatheromas, and pathologic intimal thickening. Despite there being no sex differences in major adverse cardiovascular events (MACE), NCL minimal lumen area $\leq 4 \text{ mm}^2$, TCFA, and plaque burden $\geq 70\%$ were predictive of nonculprit 3-year MACE among men, whereas only the latter two were predictive for women.¹⁴

A further subanalysis of PROSPECT evaluated sex differences in plaque characteristics and composition of 697 untreated NCLs among ACS patients aged < 65 and ≥ 65 years to further assess explanations for worse outcomes among young women despite less obstructive CAD. Men aged < 65 years had more fibroatheromas and NCLs per patient with larger plaque volumes and fewer fibrotic plaques than similarly aged women. No such sex differences were seen in those aged ≥ 65 years, although these patients overall had greater plaque burden, necrotic core, and dense calcium, potentially suggesting a differential sex-related effect on atherosclerosis progression.¹⁵

The OCTAVIA study used OCT for comparisons of culprit plaque characteristics of 140 age-matched ST-segment elevation MI patients undergoing primary percutaneous coronary intervention. Although an age-matching algorithm was used, which decreased the differences in the risk profiles between men and women, very few women aged < 50 years were included, reflecting inherent issues and challenges in obtaining representative sex-specific data in imaging-based trials. Two-thirds of culprit lesions in this study comprised atherosclerotic ruptured plaques with thrombus. Similar rates of plaque rupture were seen between men and women (50% vs 48.4%). At 9 months, there were no sex differences in strut coverage or amount of in-stent neointimal obstruction, with similar 30-day and 1-year follow-up clinical outcomes.¹⁶

Schoenenberger et al also examined the effect of age and sex on plaque burden of culprit and NCLs of 390 patients (27.6% women), one-quarter of whom presented with ACS, in a single-center Swiss study. The proximal 4 cm of all three coronary vessels were examined by VH IVUS. In nonculprit vessels in both men and women, plaque burden increased significantly with aging. Men had higher plaque burden than women at any age, although plaque morphology of nonculprit vessels was less rupture-prone. Necrotic core in nonculprit vessels among women was very low in younger age groups and increased with aging, leading to a plaque morphology similar to that of men. There were no sex differences in culprit vessel plaque morphology of young women and men. With aging, although there was no significant change in plaque burden in culprit vessels, men had increasingly rupture-prone plaque morphology, manifested as increasing percentages of necrotic core and dense calcium, as compared with women.¹⁷

In a single-center VH IVUS study of 362 ACS patients from South Korea, women were more likely to be diabetic, had greater proportions of necrotic core volume, and had a numerically higher incidence of TCFA compared with men. However, no differences in plaque components were seen between diabetic women and men and between women and men with elevated high-sensitivity C-reactive

protein (hs-CRP) levels. Also, female sex was not an independent predictor of TCFA, suggesting that sex differences in vulnerable plaque components may indeed result from greater prevalence of diabetes and hs-CRP elevation, rather than female sex. This also underscores the need for well-powered randomized controlled trials to further explore these observational findings.¹⁸

SEX DIFFERENCES IN PLAQUE VOLUME IN ACS AND CCS

The prespecified IVUS substudy from the ADAPT-DES trial included ACS and stable CAD patients and compared lesion morphology of 588 men and 192 women according to two age groups (< 65 vs ≥ 65 years). Both plaque ruptures and TCFA were more common in men versus women overall (ruptures, 36.3% vs 23%; $P < .01$; TCFA, 53.3% vs 44.7%; $P = 0.026$); however, in patients aged < 65 years (but not ≥ 65 years), sex differences in plaque rupture and the prevalence of TCFA were detected with ACS, with male sex being an independent predictor on multivariate adjustment. No sex differences were noted among those presenting with stable CAD, regardless of age. There were also no sex differences in attenuated plaques or calcific nodules.¹⁹

In pooled data of the AtheroRemo-IVUS and IBIS-3 studies, sex-specific analyses of a nonculprit coronary artery found that women had lower VH IVUS-derived plaque burden than men, irrespective of a diagnosis of stable CAD or ACS (38.1% vs 40.5% in stable CAD and 35.9% vs 38.8% in ACS, for women and men, respectively). Plaque volumes remained lower in women when corrected for body surface area, although differences were smaller and did not reach statistical significance. Standardized total plaque volume, as well as volumes of fibrous tissue, fibro-fatty tissue, dense calcium, and necrotic core were also lower in women. However, there were no sex differences in the presence of high-risk lesions, including TCFA lesions or those with plaque burden ≥ 70%. NIRS-derived LCBI was slightly lower in women, notably in stable CAD. These differences remained significant after adjustment for comorbidities.²⁰

MINOCA

Myocardial infarction with nonobstructive coronary artery disease (MINOCA) is an important entity of acute MI, particularly among women. Intracoronary imaging, either IVUS or OCT, is recommended in the workup of patients with MINOCA, as plaque disruption is not readily visible by coronary angiography.²¹

In a multicenter study of multimodality imaging (ie, OCT and cardiac MR) of 301 women diagnosed with MINOCA, an identifiable etiology of MINOCA was found in 84.5%. A definite or possible culprit lesion was identified by OCT in 46.2%, which was most commonly plaque rupture, intraplaque cavity, or a layered plaque. Although there were no comparisons with men in terms of MINOCA plaque morphology, this study showed the potential of intracoronary imaging in identifying plaque morphology and guiding medical therapy in this often underinvestigated subset of patients.²²

SEX DIFFERENCES IN PLAQUE VOLUME: ARE THERE REALLY ANY?

With increasing focus on vulnerable plaque, the need to discern sex differences in plaque volume by state-of-the-art intracoronary imaging techniques is further enhanced. In addition to limitations such as small sample size and nonrandomized study designs from which conclusions on clinical outcomes cannot be drawn, there remain variations and limitations of each specific imaging modality in the identification of plaque characteristics. VH IVUS is limited in its ability to detect plaque erosion due to limitations in spatial resolution. Some of these limitations may be overcome by the newer NIRS technology, which has greater accuracy on plaque composition based on the specific chemical characteristics of the fibroatheroma. However, NIRS is limited in that it does not provide information on the depth of data acquisition. Despite its higher axial and lateral resolution, OCT has a lower penetration depth than IVUS, making visualization of the entire depth of plaque of a lesion difficult, especially in the case of lipid-rich tissue, in which the optical signal is attenuated

significantly. Ethnicity of patients may be an additional confounder that has not been well studied. Future studies focusing on visualizing sex-related plaque changes ought to focus on this aspect, as well as combining various intravascular imaging techniques aimed at identifying vulnerable plaque at an early stage of the atherosclerotic process.

10. Risk for Ischemic Heart Disease Increased With Adverse Pregnancy Outcomes

Women with adverse pregnancy outcomes have an increased long-term risk for ischemic heart disease, according to a study published online Feb. 1 in *The BMJ*.

Casey Crump, M.D., Ph.D., from the Icahn School of Medicine at Mount Sinai in New York City, and colleagues conducted a national cohort study involving 2,195,266 women with a first singleton delivery in Sweden during 1973 to 2015 to examine the associations between major adverse pregnancy outcomes and long-term risks for ischemic heart disease.

The researchers found that 3.8 percent of the women were diagnosed with ischemic heart disease during 53.6 million person-years of follow-up. Independent associations were seen for all five adverse pregnancy outcomes (preterm delivery, small for gestational age, preeclampsia, other hypertensive disorders of pregnancy, and gestational diabetes) with an increased risk for ischemic heart disease. In the 10 years after delivery, the adjusted hazard ratios for ischemic heart disease associated with specific adverse pregnancy outcomes were 2.09, 1.72, 1.54, 1.30, and 1.10 for other hypertensive disorders of pregnancy, preterm delivery, preeclampsia, gestational diabetes, and small for gestational age, respectively. Even 30 to 46 years after delivery, the hazard ratios remained significantly increased at 1.47, 1.40, 1.32, 1.23, and 1.16, respectively. Shared familial factors partially explained these findings (<45 percent). Further increases in risk were seen for women who experienced multiple adverse pregnancy outcomes.

"Women with adverse pregnancy outcomes should be considered for early preventive evaluation and long-term risk reduction to help prevent the development of ischemic heart disease," the authors write.

11. Cumulative Exposure to Estrogen Linked to Lower Risk for Stroke

Lifetime cumulative exposure to estrogen is associated with a reduced risk for stroke, according to a study published online Feb. 1 in *Neurology*.

Leying Hou, Ph.D., from Zhejiang University School of Medicine in Hangzhou, China, and colleagues examined the associations of lifetime cumulative estrogen exposure due to reproductive factors with stroke among postmenopausal Chinese women. Lifetime cumulative estrogen exposure was assessed using three indicators: reproductive life span (RLS), endogenous estrogen exposure (EEE), and total estrogen exposure (TEE).

Data were included for 122,939 postmenopausal participants aged 40 to 79 years without prior stroke at baseline. The researchers identified 15,139 new-onset stroke cases during a median follow-up of 8.9 years, including 12,853 cases of ischemic stroke (IS), 2,580 cases of intracerebral hemorrhage (ICH), and 269 cases of subarachnoid hemorrhage. Compared with the lowest quartile of RLS, the highest quartile had a significantly lower risk for total stroke, IS, and ICH (adjusted hazard ratios, 0.95, 0.95, and 0.87, respectively). A graded association was seen for the highest versus the lowest quartile of both EEE and TEE with a subsequent descending risk for total stroke (adjusted hazard ratios, 0.85 and 0.87, respectively), IS (adjusted hazard ratios, 0.86 and 0.86, respectively), and ICH (adjusted hazard ratios, 0.73 and 0.83, respectively).

"These findings might help with new ideas for stroke prevention, such as considering screenings for people who have a short lifetime exposure to estrogen," a coauthor said in a statement.

12. CV Health Profiles Concerning in Bisexual Females, US Data Suggest

ompared with heterosexual females, those who are bisexual have less favorable scores on standardized measures of CV health, new data show. The same study, however, found that gay males tend to have better CV health profiles than their heterosexual counterparts.

Additionally, both bisexual females and gay/lesbian adults have greater exposure to nicotine—through either their own use of combustible tobacco products or by second smoke—than heterosexual adults.

“We wanted to conduct one of the first studies that would look at cardiovascular health in sexual minorities in a comprehensive manner rather than looking at individual risk factors,” said Billy A. Caceres, PhD, RN (Columbia University School of Nursing, New York, NY), who led the new study, published online February 22, 2023, in *JAMA Cardiology*. “Risk factors don’t exist in a vacuum. People who smoke . . . might also have higher risk for hypertension or diabetes, so the combination of risk factors is a greater predictor of their risk for cardiovascular disease than one factor alone.”

The new findings are in line with a growing body of research suggesting that sexual minority adults in the LGBTQ+ community have certain unique stressors, including discrimination, which may lead to worse CV health compared with cisgender, heterosexual adults. Bisexual women and gay men are about 20% more likely to be diagnosed with hypertension than heterosexual individuals, with bisexual women at higher risk of untreated hypertension.

“There is sort of a consensus in the field that bisexual individuals have greater risk for things like mental health issues and substance use, and now we’re taking that further and looking at chronic conditions like cardiovascular disease and seeing similar patterns,” Caceres told TCTMD. “It confirms and further shows us that these groups of bisexual individuals, particularly bisexual women, really

need more attention moving forward, not only in research, but also in terms of clinical interventions.”

The reasons why bisexual females have worse CV health in relation to all other groups, including bisexual males, is likely multifactorial but may be partially explained by high rates of living in poverty relative to other sexual identity groups or delaying healthcare for financial reasons, both of which may lead to less preventive screening for CVD and other chronic conditions.

“Other work has found that [bisexual women] are more likely to report that they can't seek healthcare because of reasons that have nothing to do with cost. Things like they didn't have proper transportation, they couldn't take time off work, etc,” Caceres added. “We also know that overall—and this is true for both bisexual women and lesbian women—the field of sexual minority health has had a larger focus on HIV and AIDS, with [emphasis on] gay and bisexual men.”

With research about the intersection of sexual identity and health so relatively new, he said, many bisexual and lesbian women also probably have no idea about studies on risk factors that are being done in their own populations.

Elevating Patient Discussions

For the study, Caceres and colleagues used the American Heart Association's recently revised Life's Essential Eight, which assesses poor, intermediate, or ideal CV health based on specific metrics : dietary quality, physical activity, exposure to cigarette smoking, body mass index (BMI), fasting blood glucose, total cholesterol, blood pressure, and the newly introduced element of sleep.

Scores were analyzed for 12,180 adults (mean age 39.6 years; 49.5% female; 11.1% Black, 15.7% Hispanic) in the National Health and Nutrition Examination Survey (NHANES). Participants self-reported current and lifetime combustible tobacco use and secondhand smoke exposure, frequency and duration of weekly moderate and vigorous physical activities, diet quality, and sleep duration, while

biological measures were assessed using standardized assessments. Cumulative ideal CV health scores were categorized as low (0-49), moderate (50-79), or high (80-100).

Overall, bisexual females had less favorable BMI and lower cumulative ideal CV health scores (< 50) compared with heterosexual females. There were no differences in ideal CV health scores for lesbian females and females with other sexual identities in comparison to heterosexual females, and no differences between other groups of sexual minority adults and their heterosexual counterparts.

Bisexual males were more likely than heterosexual males to have hypertension (adjusted OR 1.98; 95% CI 1.10-3.56) and to be prescribed antihypertensive medications (adjusted OR 2.20; 95% CI 1.12-4.32).

Compared with heterosexual men, gay males had more favorable diet, BMI, and glycemic status scores, although they had higher rates of tobacco use. While the reasons for these outcome differences are unclear, Caceres and colleagues say they may align with documented desires to conform to body ideals of thinness, excessive exercising, and dieting among gay men.

By people being able to have open conversations around sexuality and [their] personal lives, it might uncover things that otherwise wouldn't be acknowledged.Billy A. Caceres

According to Caceres, incorporating discussions about sexual orientation and gender identity into routine healthcare intake assessments is a slowly growing trend that will help in earlier identification of specific CV risks.

“As providers, I think there is so much more of our own discomfort with getting into topics around sexuality in a context that don't necessarily have to do with sexuality than there is for patients,” Caceres added.

For bisexual patients, who often feel stigmatized and like they don't belong in gay, lesbian, or heterosexual communities, this may be a particularly crucial step in their health journey.

“There may be a lack of awareness about the true health impacts of some of the behaviors or things that they're engaging in, and by people being able to have open conversations around sexuality and [their] personal lives, it might uncover things that otherwise wouldn't be acknowledged,” Caceres added.

12. LAAO Tops Oral Anticoagulation for AF in Women and Men: Medicare Analysis

edicare beneficiaries with atrial fibrillation (AF) see better long-term outcomes when they undergo left atrial appendage occlusion (LAAO) rather than receive oral anticoagulation, a new analysis shows. But the observational study has limitations that may make it difficult to draw firm conclusions.

Through an average follow-up of about a year, risks of mortality and stroke/systemic embolism were lower in both women and men treated with LAAO versus oral anticoagulation, researchers led by Emily Zeitler, MD (Dartmouth Health, Lebanon, NH), report in a study published in the February 14, 2023, issue of *Circulation*.

Bleeding was increased in the LAAO group early on, but after a 45-day periprocedural period, bleeds were more frequent in the anticoagulation group, regardless of patient sex.

This information can be useful in shared decision-making discussions with patients, particularly women, who have been underrepresented in LAAO trials, study co-author Megan Coylewright, MD (Erlanger Health System, Chattanooga, TN), told TCTMD. She noted that the advantages for LAAO over anticoagulation

were seen despite the fact that patients who underwent the procedure were sicker overall, which is consistent with what she sees in clinical practice.

“That’s helpful when I’m talking to my patients—to share that there is a potential for benefit with regards to stroke and bleeding and death in the option of LAAO for those that have an appropriate rationale not to take a long-term blood thinner,” Coylewright said.

I can say it is a reasonable option for those patients who have an elevated risk of bleeding or a history of prior bleeding.Megan Coylewright

The data also provide additional information specifically for women, who have been shown in prior studies to have greater risks of stroke and bleeding related to AF and more complications associated with LAAO compared with men. In 2021, the US Food and Drug Administration said it was looking into potential sex-based difference in LAAO complications.

When speaking with women today, “I share with them that they have two options—both are reasonable, they have different pros and cons—and I listen to what’s most important to the patients,” Coylewright said. “And usually people who are referred to me have a history of fairly severe bleeding or high bleeding risk for which oral anticoagulation is not a good option in the long term. And so I feel this data provides reassurance that there is the possibility for great benefit with this alternative—that is, left atrial appendage occlusion.”

Commenting for TCTMD, Mohamad Alkhouli, MD (Mayo Clinic, Rochester, MN), said the study addresses an important question, but he highlighted several limitations that muddy interpretation of the results.

“Conceptually, I think it is very hard to answer this question from observational data, and even if you do get some hint, it’s mostly hypothesis-generating, so you can’t really be conclusive unless you have a trial,” he said, noting that there are

several ongoing RCTs comparing LAAO and oral anticoagulation for stroke prevention in AF.

In the current analysis, Alkhouli pointed to residual confounding and the inability to ensure adequate propensity matching; selection bias stemming from who was offered LAAO and how the index time point was selected for the anticoagulation group; and the lack of a competing-risk analysis.

“It’s hard to come up with any solid conclusions given some of the methodological issues and the inability to adequately control for residual confounders,” Alkhouli said. “We should be patient and wait for the randomized trials with their long-term outcomes that are coming. Observational studies are useful as hypothesis-generating, but we should not overstate their conclusions because they have nonremediable limitations.”

Bolstering LAAO Data Specific to Women

Much of the debate around the efficacy and safety of LAAO revolves around the fact that there have been changes in practice since the initial trials were performed. The early studies of LAAO using the first-generation Watchman device (Boston Scientific) had warfarin as the comparator, but since then, direct oral anticoagulants (DOACs) have taken over as the preferred choice.

Moreover, patients that have been treated with LAAO outside of trial settings tend to be older and to have more comorbidities, and they are more likely to be women, who were underrepresented in the pivotal trials. In the initial Watchman trials, in fact, about 70% of participants were men, and only 224 women were implanted with the device in randomized trials before the technology was approved by the FDA in 2015.

That, along with data showing worse short-term LAAO outcomes among women versus men, provided the inspiration to gather more data specific to women to inform daily decision-making, Coylewright said.

For the current study, Zeitler, Coylewright, and colleagues examined Medicare fee-for-service claims data spanning 2015 to 2019 and used propensity scores to match those treated with LAAO and those treated with oral anticoagulation. After matching, the analysis included 4,085 patient pairs among women (mean age 76; mean CHA₂DS₂-VASc score 5) and 5,378 among men (mean age 75; mean CHA₂DS₂-VASc score 4).

Through follow-up, LAAO was associated with a significant reduction in mortality among women (HR 0.51; 95% CI 0.45-0.58) and men (HR 0.54; 95% CI 0.49-0.60), with similar differences observed for stroke/systemic embolism among women (HR 0.66; 95% CI 0.56-0.77) and men (HR 0.65; 95% CI 0.55-0.76).

Bleeding risk varied over time, however. It was higher in the LAAO group within the initial 45-day periprocedural period, during which the recommended antithrombotic strategy was a combination of anticoagulation and aspirin. After that point, LAAO was associated with lower bleeding risks in both women (HR 0.77; 95% CI 0.68-0.88) and men (HR 0.88; 95% CI 0.78-0.99).

The researchers also included a couple of falsification endpoints—shingles and osteoarthritis—to evaluate the potential for residual confounding. The analysis “failed to detect a difference in groups but does not rule out that one exists,” they write.

Addressing Limitations

The investigators acknowledge that the analysis has some limitations, but point out that “other observational comparative analyses of LAAO and contemporary anticoagulation strategies have demonstrated similar findings, and preliminary data suggest benefits of LAAO over anticoagulation when delivered exclusively with DOACs overall and in sex subgroups.”

They add that “future randomized data are forthcoming to better define this comparative relationship in all comers.”

Coylewright said she'd like to see more discussions of the limitations of randomized trials—namely, their lack of representation of the types of patients seen in everyday practice.

We should be patient and wait for the randomized trials with their long-term outcomes that are coming.Mohamad Alkhoul

“We as a community will need to continue to focus on making sure our research is representative of the patients who we’re seeing in clinic every day,” she said, noting that when there more diversity in the physician workforce and clinical trial leadership, recruitment of women into clinical trials is improved.

Cardiology, however, has had a hard time recruiting and retaining women, Coylewright said. “In part, it’s because in the past . . . we’ve had somewhat of a toxic culture. The work we do to take care of patients and reduce their risk of stroke is difficult work, and the only way that we can move forward together as a field is through respectful and professional interactions to raise the bar.”

As for the issues raised around the current study, Coylewright said, “All of our research has limitations. It’s true. We don’t deny that observational data are limited, and it really is just one piece of information in a broader literature around left atrial appendage occlusion in stroke prevention.”

But it’s a piece that helps fill in some of the gaps in knowledge about LAAO, she said. “There’s a little bit more information specific to women that left atrial appendage occlusion is an option. I wouldn’t say that I can use observational data to definitively say what the magnitude of benefit is, but I can say it is a reasonable option for those patients who have an elevated risk of bleeding or a history of prior bleeding. And I think it’s really important that our patients have choices.”

13. Pregnancy in Women With Congenital Heart Disease and Pulmonary Hypertension

Study Questions:

What are outcomes for pregnancy in women with congenital heart disease (CHD) with and without pulmonary hypertension (PH)?

Methods:

Outcomes for women with CHD were evaluated retrospectively from 1993 to 2016 and prospectively from 2017 to 2019 at seven tertiary centers in China. Diagnosis of PH was based on echocardiogram or catheterization. The incidence of maternal death, cardiac complications, and obstetric and offspring complications was compared for women with CHD and no PH, mild PH, and moderate-to-severe PH.

Results:

A total of 2,220 pregnant women with CHD had completed pregnancies. PH associated with CHD was identified in 729 women. Mild PH (right ventricle [RV] to right atrium [RA] gradient 30-50 mm Hg) was present in 398 women, while moderate PH (RV to RA gradient >50 mm Hg) was present in 331. Maternal mortality occurred in one (0.1%) woman with no PH, no women with mild PH, and 19 (5.7%) women with moderate-to-severe PH. Overall, patients with mild PH had better maternal outcomes than those with moderate-to-severe PH. Obstetric complications occurred in 5.3% of women with mild PH as compared with 15.7% of women with moderate-to-severe PH ($p < 0.001$). B-type natriuretic peptide (BNP) >100 ng/L and New York Heart Association (NYHA) class III-IV were independently associated with adverse maternal cardiac events, while follow-up with a multidisciplinary team and strict antenatal supervision were protective.

Conclusions:

Women with CHD and mild PH appear to have better pregnancy outcomes as compared with those with moderate-to-severe PH.

Perspective:

Pregnancy in women with PH has historically been associated with extremely high (approaching 50%) mortality, although outcomes have improved in recent years. This multicenter study showed improving maternal outcomes and demonstrated the heterogeneity of this disease process, with significantly better outcomes for women with CHD and mild PH as compared with those with moderate-to-severe PH. Pregnancy termination or miscarriages occurred in a relatively high proportion of pregnancies with moderate-to-severe PH (494 out of 825), which raises the possibility that sicker patients underwent termination. Additionally, the overall favorable outcomes seen in this study occurred in the setting of an extremely high rate of Caesarean delivery (83-92% based on severity of PH). The optimal mode of delivery for patients with CHD and PH remains unclear. Overall, this study suggests a role for individualized counseling for patients regarding risks, and meticulous, multidisciplinary team-based care for patients with CHD and PH contemplating or undergoing pregnancy.