News in April 2023

1. Certain Reproductive Factors Play Causal Role in CVD for Women

Reproductive factors play a causal role in cardiovascular disease (CVD) in women, according to a study published online Feb. 27 in the Journal of the American Heart Association.

Maddalena Ardissino, M.B.B.S., from Imperial College London, and colleagues examined the causal role of reproductive factors on cardiovascular disease in women using Mendelian randomization. Uncorrelated, genome-wide significant single-nucleotide polymorphisms were extracted from sex-specific genome-wide association studies.

The researchers found that earlier genetically predicted age at first birth increased the risk for coronary artery disease, heart failure, and stroke (odds ratios per year, 1.49, 1.27, and 1.25, respectively); partial mediators included body mass index, type 2 diabetes, blood pressure, and cholesterol traits. The risks for atrial fibrillation, heart failure, ischemic stroke, and stroke were increased with a higher genetically predicted number of live births (fewer than two versus two versus more than two: odds ratios, 2.91, 1.90, 1.86, and 2.07, respectively). Increased risks for coronary artery disease and heart failure were seen with earlier genetically predicted age at menarche (odds ratios per year, 1.10 and 1.12), with both associations partially mediated by body mass index.

"The findings support the emerging research focus on female-specific risk factors for CVD, by demonstrating that earlier first birth, higher number of live births, and earlier menarche are all associated with increased CVD in women," the authors write. "We stress the importance of routine evaluation of reproductive history in clinical risk stratification and consideration of targeted prevention strategies for women."

2. Incidence of Cardiac Arrest During Sports Among Women in the European Union

BACKGROUND

Women represent a growing proportion of sports participants. Still, few original data regarding sudden cardiac arrest during sports (Sr-SCA) in women are available.

OBJECTIVES

The authors sought to assess the incidence, characteristics, and outcomes of women presenting with Sr-SCA.

METHODS

Data were analyzed from 3 population-based European registries (ESCAPE-NET 2020 Horizon Program) that prospectively and exhaustively collect every case of SCA: SDEC (Paris-Sudden Death Expertise Center), ARREST (AmsteRdam REsuscitation Studies), and SRCR (Swedish Register for Cardiopulmonary Resuscitation). Sr-SCA was defined as SCA during or ≤1 hour after cessation of sports activity.

RESULTS: Of 34,826 SCA between 2006 and 2017, 760 Sr-SCA (2.2%) were identified, including 54 in women. The average annual incidence of Sr-SCA in women in the 3 registries ranged from 0.10 per million (95% CI: 0.01-0.71 per million) to 0.38 per million (95% CI: 0.14-1.04 per million). Overall, the average annual incidence rate of Sr-SCA in women was 0.19 per million (95% CI: 0.14-0.24 per million), >10-fold lower compared with men (2.63 per million [95% CI: 2.45-2.83 per million]; P < 0.0001). When extrapolating to the total European population and accounting for age and sex, this yields 98 cases per year (95% CI: 72-123 cases per year) in women and 1,350 cases per year (95% CI: 1,256-

1,451 cases per year) in men. Subject characteristics and circumstances of occurrence were similar in women vs men. Bystander response, time to defibrillation, and survival rate at hospital admission (58.8% vs 58.5%; P = 0.99) and 30 days did not differ significantly between women and men.

CONCLUSIONS

These findings emphasize the dramatically lower risk of Sr-SCA in women compared with men, despite similar subject characteristics. This should be considered in designing preparticipation screening strategies in the future.

3. Blood Levels of Angiotensinogen and Hypertension in the Multi-Ethnic Study of Atherosclerosis (MESA)

Background

Angiotensinogen is the proximal precursor of the angiotensin peptide hormones of the renin-angiotensin-aldosterone system (RAAS). Clinical trials are ongoing targeting angiotensinogen for the treatment of hypertension and heart failure. The epidemiology of angiotensinogen is not well defined, particularly its relationship to ethnicity, sex, and blood pressure (BP)/hypertension.

Objectives

The authors sought to determine the relationship of circulating angiotensinogen levels to ethnicity, sex, BP, incident hypertension, and prevalent hypertension in a modern sex-balanced ethnically diverse cohort.

Methods

Plasma angiotensinogen levels were measured in 5,786 participants from the MESA (Multi-Ethnic Study of Atherosclerosis). Linear, logistic, and Cox proportional hazards models were utilized to examine the associations of angiotensinogen with BP, prevalent hypertension, and incident hypertension, respectively.

Results

Angiotensinogen levels were significantly higher in females than males and differed across self-reported ethnicities with the ordering (from highest to lowest): White, Black, Hispanic, and Chinese adults. Higher levels were associated with higher BP and odds of prevalent hypertension, after adjusting for other risk factors. Equivalent relative differences in angiotensinogen were associated with greater differences in BP in males vs females. In males not taking RAAS-blocking medications, a standard deviation increment in log-angiotensinogen was associated with 2.61 mm Hg higher systolic BP (95% CI: 1.49-3.80), while in females the same increment in angiotensinogen was associated with 0.97 mm Hg higher systolic BP (95% CI: 0.30-1.65).

Conclusions

Significant differences in angiotensinogen levels are present between sexes and ethnicities. A positive association is present between levels and prevalent hypertension and BP, which differs between sexes.

4. CVD and Mortality in Black Women Carriers of the TTR V122I Variant

BACKGROUND

Long-term data on cardiovascular disease (CVD) and mortality in female carriers of the transthyretin (TTR) V122I (pV142I) variant, one of the most common variants of hereditary transthyretin cardiac amyloidosis, are sparse and the effects of blood pressure, heart rate, body mass index, and physical activity on CVD outcomes remain largely unknown.

OBJECTIVES

The aim was to first examine the relationship of TTR V122I (pV142I) carrier status with CVD and mortality and second to investigate the effects of blood pressure, heart rate, body mass index, and physical activity in a large cohort of postmenopausal women.

METHODS

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

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

CONCLUSIONS

Black female TTR V122I (pV142I) carriers have a higher CVD and all-cause mortality risk compared to noncarriers. In case of clinical suspicion of amyloidosis, they should be screened for TTR V122I (pV142I) carrier status to ensure early treatment onset.

5. Later-Life Mortality Increased With Pregnancy Complications

Pregnancy complications are associated with increased mortality in later life, according to a study published online March 28 in Circulation.

Stefanie N. Hinkle, Ph.D., from the University of Pennsylvania in Philadelphia, and colleagues examined pregnancy complications in association with total and cause-specific mortality in 46,551 participants (45 and 46 percent Black and White, respectively). Adjusted hazard ratios for underlying all-cause and cause-specific mortality were estimated for preterm delivery (PTD), hypertensive disorders of pregnancy, and gestational diabetes/impaired glucose tolerance (GDM/IGT). The median time between index pregnancy and death/censoring was 52 years.

The researchers found that mortality was higher among Black than White participants (41 versus 37 percent). Of the participants, 15, 5, and 1 percent had PTD, hypertensive disorders of pregnancy, and GDM/IGT, respectively. The incidence of PTD was higher in Black versus White participants (20 versus 10 percent). Associations with all-cause mortality were seen for preterm spontaneous labor, preterm premature rupture of membranes, preterm induced labor, and preterm prelabor cesarean delivery versus full-term delivery (adjusted hazard ratios, 1.07, 1.23, 1.31, and 2.09, respectively); gestational hypertension, preeclampsia or eclampsia, and superimposed preeclampsia or eclampsia compared with normotension (adjusted hazard ratios, 1.09, 1.14, and 1.32, respectively); and GDM/IGT versus normoglycemia (adjusted hazard ratio, 1.14).

Greater mortality risk in association with preterm induced labor was seen for Black versus White participants (adjusted hazard ratios, 1.64 versus 1.29).

"The value of these data is that they provide more inclusive findings, extending what has been mostly limited to predominately White samples to Black pregnant people, as well," Hinkle said in a statement.

6. Similar Outcomes in Men and Women After Transcatheter Tricuspid Interventions

Men and women have different underlying causes of severe tricuspid regurgitation (TR), but transcatheter interventions can successfully be performed in both sexes and result in similar survival out to 2 years, according to the results of an observational study.

Researchers also identified several predictors of mortality, noting that NYHA functional class, tricuspid annulus plane systolic excursion (TAPSE), which is a measure of right ventricular function, and mean pulmonary artery pressure (mPAP) identified patients most likely to survive the procedure.

“It’s still a relatively new field,” senior investigator Volker Rudolph, MD (Heart and Diabetes Center North Rhine-Westphalia, Germany), told TCTMD. “As an overall cohort, these patients have a lot of comorbidities, so you’re always trying to make the decision—will there be a benefit if we do this procedure? It’s important for us to understand that. Of course, the procedure has such low risk you can do it virtually in anyone, but you want to only do it in patients who will benefit. We want to know who’s going to gain the most.”

While the predictors of survival weren’t too surprising, Rudolph said their study goes one step further in that they identified different thresholds for right ventricular-pulmonary arterial coupling, which is a measure how well the right

ventricle has adapted to the resistance of the pulmonary arterial system. This is expressed as the ratio of TAPSE to mPAP.

“The lower the ratio, the worse the prognosis of the patient,” he said. “It should be around 0.80. If it gets lower, it tells you there’s a problem and the right ventricle tends to decompensate. We found that when looking at these parameters against the background of sex, the ideal cutoff to predict survival was very different between and women.”

The new study, which was led by Vera Fortmeier, MD (Heart and Diabetes Center North Rhine-Westphalia), was published online April 5, 2023, ahead of print in JACC: Cardiovascular Interventions.

Men More Likely to Have CAD

Transcatheter tricuspid valve intervention (TTVI), encompassing both repair and replacement of the tricuspid valve, is relatively novel compared with transcatheter treatment of the aortic and mitral valves, but there are a number of technologies in development for patients who can’t undergo surgery. Last month at the American College of Cardiology/World Congress of Cardiology (ACC/WCC) meeting, investigators presented results of the randomized TRILUMINATE Pivotal study showing that transcatheter edge-to-edge repair (TEER) safely and effectively treated patients with severe TR, a benefit that was driven by quality-of-life improvements.

To TCTMD, Rudolph said past studies have identified sex-related differences in the underlying etiology and prognosis of TR in its natural course. Men with significant TR are more likely to have concomitant coronary artery disease and often present with worse left ventricular function. Data also suggest that men fare worse with respect to survival at 10 years, the researchers say. To date, though, no study has looked at whether these comorbidities and TR etiology

affect procedural success and long-term survival, potentially leading to differences in benefits by sex.

The group studied the outcomes of 386 women and 316 men with symptomatic severe TR treated with TTVI between 2016 and 2021 at multiple European centers. Men were more likely than women to have predominantly secondary ventricular TR (64.6% vs 50.0%), while women were more likely to have secondary atrial TR (41.7% vs 24.4%).

With ventricular TR, the right ventricle is dilated and/or dysfunctional, with the valve pulled into the ventricle, resulting in "tenting and tethering," said Rudolph. On the other hand, "atrial regurgitation, where you just have a dilated annulus without tethering, which is seen as an easier morphology to treat, was much more common in women," he said. "From these data, you might have suspected that procedural results might be better in women compared with men, but that wasn't the case."

Procedural success—defined as TR reduction by at least one grade—was 90.9% in women and 91.8% in men (P = 0.796). Mortality also didn't differ, with 69.9% of women and 63.7% of men still alive 2 years after TTVI (P = 0.144).

Abdel Almanfi, MD (Baylor St. Luke's Medical Center, Houston, TX), who wasn't involved in the study, said patients with severe TR can be extremely symptomatic, with limited treatment options for those turned down for surgery. To date, no transcatheter tricuspid intervention is approved in the United States, but there are multiple options available in Europe, including devices focused on repair and replacement.

To TCTMD, Almanfi agreed that TR resulting from atrial enlargement should be easier to deal with as an operator. "I would rather deal with a diseased atrium and a healthy ventricle than deal with a diseased ventricle, or both," he said. "When the ventricle fails, it's often late-stage and it might be difficult to get the

ventricle back." The new study, though, provides some reassurances that men and women fare equally well with TTVI despite different etiologies. "If you fix the tricuspid regurgitation, survival is the same after 2 years," Almanfi told TCTMD. "Despite the different disease processes, it's the same outcome, which is really interesting."

It Can be Done, But Will it Work?

Dysfunctional right ventricular-pulmonary arterial coupling is usually measured by the ratio of TAPSE to systolic PAP (sPAP), but Rudolph pointed out that determining sPAP is prone to error in the setting of severe TR, adding that it is frequently underestimated. Instead, they used TAPSE/mPAP, which in their study was better able to predict the risk of death at 2 years compared than TAPSE/sPAP (AUC 0.672 vs 0.602; P = 0.011).

In a multivariate risk-prediction model, right ventricular function expressed by TAPSE was a very strong predictor of mortality in women but mPAP was a stronger predictor of death in men. Overall, TAPSE/mPAP was associated with mortality independent of baseline clinical, laboratory, echocardiographic, and hemodynamic variables.

The procedure has such low risk you can do it virtually in anyone, but you want to only do it in patients who will benefit. Volker Rudolph

Overall, TAPSE/mPAP levels were significantly higher in women than in men (0.650 versus 0.579 mm/mm Hg; P = 0.006), but the analysis revealed different sex-specific thresholds for the TAPSE/mPAP ratio to predict mortality. In women, a ratio less than 0.612 mm Hg was associated with increased risk of death at 2 years after TTVI compared with less than 0.434 mm Hg in men. Women with a TAPSE/mPAP ratio less than the identified threshold had a nearly 3.5-fold higher risk of death at 2 years, while men with a ratio less than 0.434 mm Hg had a twofold higher risk of death.

The different thresholds are important for determining who would benefit from treatment, say researchers.

“As we approach these patients, and as we move into individualized medicine, the [thresholds] are a huge difference,” said Rudolph. “If you’re below the cutoff, you’re at a higher risk of death, but if you use the same cutoff for men and women, you’ll come to the wrong conclusion.”

Right now, Almanfi only refers patients with symptomatic severe TR ineligible for surgery to centers participating in the clinical trials, but these new data are informative. “The ratio is really nice,” he said, noting that it provides clinical value by helping identify patients who might benefit most from TTVI. Even without the availability of transcatheter options, Almanfi said he’ll pay more attention to the prognostic information gleaned from TAPSE and mPAP.

Validation in Other Cohorts

In an editorial, Georg Nickenig, MD, and Atsushi Sugiura, MD, PhD (both University Hospital Bonn, Germany), say that these data align with those reported in the TriValve registry that also showed no significant difference in mortality between men and women treated with TTVI. Importantly, they point out, it remains unclear if TTVI improves the survival of TR patients in general. In the TRILUMINATE Pivotal study, there was no survival benefit with TEER.

The editorialists congratulate the study authors on showing the prognostic significance of right ventricular-pulmonary artery coupling based on sex, noting that right ventricular function and pulmonary circulation are interdependent. While these measures are easily obtained on echocardiography and with a right-heart catheterization, the sex-specific cutoffs will need to be validated in future analyses, they add.

“Given the inherent selection bias for TTVI, it would be imperative to investigate the value and predictive power of TAPSE/mPAP in an all-comers population with

TR," write Nickenig and Sugiura. "Only then could this parameter be used in the guidance of patient selection and the timing of intervention."

7. First-Ever Cardiac Surgery Trial in Women Poised to Launch: ROMA-Women

Hopes are high that the ROMA trial may finally answer the question of whether multiarterial grafts are better than a single arterial graft in patients undergoing primary isolated nonemergent CABG. But the trial is on track to enroll just 15% women, a group already less likely to be referred for CABG in the first place, more likely to have worse outcomes if they do, and less likely to receive guideline-directed surgical care.

Enter ROMA-Women: the first-ever cardiac surgery trial in women. With a unique, nested trial design that will leverage the infrastructure and recruiting sites of the primary ROMA trial—even repurposing the data from female patients randomized in ROMA—the trial is powered to get a decisive answer in women.

"ROMA, the parent trial, will stop enrollment on April 14th, and then on April 15th, the sites that are doing ROMA will transition to ROMA-Women," Mario Gaudino, MD, PhD (Weill Cornell Medicine, New York, NY), one of the principal investigators, explained to TCTMD. Gaudino is also the lead author of a perspective describing the design and rationale of ROMA-Women published this week in Circulation.

"Also, we are opening many more sites because we will need more enrollers," he added, noting that women make up just one-third of the overall population being referred for bypass surgery, "which is also intrinsically wrong," he said.

The chronic under-enrollment of women in clinical trials—as well as the lack of representation of minority groups, and, most notably, minority women—is a long-standing problem in medicine, formally recognized in the National Institutes

of Health (NIH) Revitalization Act in 1993. Explanations, excuses, and justifications abound, but 30 years later, women still make up less than one-third of the participants in cardiovascular clinical trials, despite accounting for roughly half of the annual CVD deaths in the US.

An Innovative Approach

For the specific question of multiarterial versus single arterial grafts, there are good reasons to think the ROMA results might differ in men and women, Gaudino and colleagues note in their paper. Women have different operative risk profiles at baseline, their operations are often more technically complex, and their procedural risks are higher. Physiologically, women have smaller coronary arteries and conduits that are more prone to spasm, a higher prevalence of microvascular dysfunction, and more varicose or diseased saphenous veins that make for lower-quality venous grafts.

There is really an urgency in the cardiac surgery community to try to understand why women do not do as well as men. Mario Gaudino

While other groups have proposed just capping the enrollment of men in trials when sufficient numbers are reached and thereafter randomizing women only, ROMA-Women represents an alternative approach that is "very innovative and exciting," said Roxana Mehran, MD (Icahn School of Medicine at Mount Sinai, New York, NY), a co-author of the Circulation perspective and a founder of Women as One, one of the groups that endorsed the study along with a wide range of professional societies and the patient-centered WomenHeart organization. "The Lancet Commission [on women] has also endorsed this and we're just very, very excited to be a part of this going forward," Mehran said.

ROMA-Women's novelty lies in the fact that it will leverage the infrastructure already in place for ROMA, including clinical trial units, database, case report forms, randomization system, site-training resources, informed consent forms,

regulatory approvals, centralized event review committee and processes, and enrolling sites—although these, as noted, will be expanded for ROMA-Women. Statistical contingencies are built into the analysis plan to reduce any cohort effects of combining data from the parent and offspring trials.

Equity in Research

In recent decades, national and international funding agencies have issued statements and proposed plans for reducing inequities in biomedical research.

“So why is it 2023 and we’re still talking about this?” asked C. Noel Bairey Merz, MD (Cedars-Sinai Heart Institute, Los Angeles, CA), a longtime advocate for addressing sex- and gender-based research inequalities and a co-author of the Circulation perspective.

In the US, Research for All legislation was passed in 2016, encouraging representative numbers of women and minorities in federally funded research, and an NIH policy amendment went into effect in 2017 stipulating that NIH-funded trials should include adequate representation of women and minority groups. But neither have teeth to require specific criteria to be filled on the basis of sex and gender, explained Bairey Merz.

This is the first time that, to my knowledge, we've tried to do something like this, so it could fail. That's why they call it research, right?C. Noel Bairey Merz

That’s in contrast to the approach of the Canadian Institutes of Health Research (CIHR), one of the original funders of ROMA—Stephen Fremes, MD (University of Toronto/Sunnybrook Health Sciences Centre, Canada), is the other principal investigator and a co-author of this week’s perspective. The CIHR is much “more progressive,” said Bairey Merz. The CIHR created an Institute of Gender and Health more than two decades ago and requires researchers submitting grant

proposals, as well as the people reviewing them, to complete mandatory training modules for integrating sex- and gender-based research.

Moreover, the proposals themselves must contain compulsory sex- and gender-based analysis (SGBA) questions, with grading of the planned SGBA forming part of grant review. In the US, said Bairey Merz, inclusion of sex- and gender-based analysis plans are not mandatory. “They strongly encourage it, but they still do not have [them] as line items,” Bairey Merz explained to TCTMD.

Gaudino, to TCTMD, agreed that the “well-intended” US legislative and NIH statements have not solved the problem of inequitable representation in US trials, but they have led to a shift. “They have at least the very important merit of having highlighted this situation and having people like me thinking, ‘Well, that's a problem.’”

Shining a Bright Light

Whether this offspring trial is any better than other ideas for making clinical trials more representative remains to be seen—there are many other factors that influence whether or not patients are encouraged to enroll or have the support in place to participate.

“This is the first time that, to my knowledge, we've tried to do something like this, so it could fail,” said Bairey Merz. “That’s why they call it research, right? If it succeeds, and it looks very feasible, then it could be a model [for other trials], because we're all struggling with the expense of doing these studies.”

Whichever way you look at it, whether it's a potential benefit or harm, it just is very, very important to make sure that women are represented. Roxana Mehran

Gaudino agreed. “The reason why I'm excited about ROMA-Women is because if it works, then it can be a model that can be adapted to essentially every other

trial where you think that there is a group of patients where the result may be different than what you see in the general population."

That's key, he continued: "There is really an urgency in the cardiac surgery community to try to understand why women do not do as well as men. If in other areas, if there is not the same sense of urgency, then probably this trial design will not get a lot of traction, even though if you don't look, you will never know. . . . In the case of coronary surgery in women, we know well that at least there are very strong reasons to believe that what we see in men is not what is happening in women. So why would you combine these two different populations in the same trial? In the end, the overall result that you get will just be the mean or the average between what happened in one population and what happened in the other population, so essentially it will be meaningless for both populations."

Not only is it important to think "a priori" about trials in which a given intervention might yield unique benefits in women, but also it's critical to study which might be harmful, Mehran pointed out. "Whichever way you look at it, whether it's a potential benefit or harm, it just is very, very important to make sure that women are represented."

She cited two other efforts underway that might lead to more-equitable clinical trial representation. In the first, the Academic Research Consortium (ARC), which has previously collaborated on bleeding risk and valve intervention endpoint definitions, "is taking on the whole idea of diversity in clinical trials and how to implement diversity—really thinking outside of the box to come up with trial designs as well as definitions for ARC-Diversity," she said.

"Then the second part is that the Lancet Commission this whole year, 2023, will be mobilizing several think tanks to discuss clinical trials in women for topics that are very much prevalent, where we have very little data in women. So, we will be doing some more all-female studies going forward."

Bairey Merz agreed there's more work to be done.

"To generate policy, [we need] advocacy—shining a bright light and just being persistent and not saying, 'Oh well, that's the way it's just always going to be,'" she said. "It's that tipping effect. Sometimes it seems like the world is going backwards right now for women . . . but if we think back 20 years ago, 30 years, 40 years ago, things were worse. Progress is sometimes tiny."

8. AHA Urges Holistic Cardiovascular Care of Women, With Focus on Race/Ethnicity

ith a focus on treating the whole woman, and not simply single facets of her cardiovascular health, a new American Heart Association (AHA) statement emphasizes the need to take into account racial and ethnic differences in cardiovascular risk factors as well as promote preventive therapies for women in the United States. These nuances, its authors say, will help improve women's care across the board.

"This scientific statement is just a small brushstroke in the whole landscape of women's cardiovascular health and the impact and intersection with race and ethnicity," writing committee chair Laxmi S. Mehta, MD (The Ohio State University, Columbus), told TCTMD. "There is a lot that has to be done and we hope we have tickled people's interest into the area, not just as clinicians, but as learners that are out there and as [researchers]."

Especially among Black women, Mehta continued, there are a "lot of social determinants of health that impact them, and so we need to be advocating for reforms that can improve their health and acknowledging the nonbiological factors."

"This statement definitely is a call to action to have the medical community use a much wider lens to look at this differently," echoed Jennifer H. Mieres, MD

(Northwell Health, Lake Success, NY), who served as vice chair of the writing committee. She stressed to TCTMD that the publication of this document during National Minority Health Month was a conscious choice, and reminded clinicians not to simply base decisions on risk calculators because these tools don't include social determinants of health.

"For the woman in front of you, you need to really find out what matters to her and really understand what her living conditions are like," said Mieres.

For the woman in front of you, you need to really find out what matters to her and really understand what her living conditions are like. Jennifer H. Mieres

Commenting on the statement for TCTMD, Fatima Rodriguez, MD (Stanford University School of Medicine, CA), commended the authors "for emphasizing that race and ethnicity are sociocultural constructs that impact the way that women experience cardiovascular health and disease across the life course." Given the heterogeneity—especially for women—within various racial and ethnic categories in terms of CVD risk and outcomes, the "intersectionality of race, ethnicity, and sex can compound health disparities," Rodriguez said in an email, adding that Black women tend to experience the greatest disparities.

While this statement follows others discussing CVD prevention in women more broadly, it "is important because it directly calls out the importance of the nonbiological factors of race and ethnicity and cardiovascular disease risk," she continued.

The statement was published online today in Circulation on behalf of the AHA Cardiovascular Disease and Stroke in Women and Underrepresented Populations Committee.

Focus on Nonbiological Risk Factors

In the statement, Mehta, Mieres, and colleagues outline the current available evidence on CVD for several racial ethnic groups, including Black, Hispanic/Latina, American Indian and Alaska Native, and Asian women. They also explore the most common CVD risk factors for women in general, including hypertension, dyslipidemia, diabetes, obesity, and tobacco use.

Digging into nontraditional risk factors, the statement explores what impact a variety of social determinants of health can have on CVD diagnosis and outcomes, with an eye toward how several of these affect different populations differently.

While the writing committee acknowledges "notable progress" has been made for the prevention and treatment of CVD for women across the board in the US, several gaps still need to be addressed. They call for broader representation of women in tools like the American College of Cardiology/AHA Pooled Cohort Equation as well as "specific lifestyle recommendations tailored to cultural norms and behaviors" embedded in CVD prevention guidelines.

Future improvements will likely be found through partnerships with "community-based approaches, faith-based community partnerships, and peer support," according to the writing committee. "Key considerations in providing culturally competent care are the patient's preferred language and religion, dietary restrictions, sex identity, cultural norms and practices, health literacy, and cultural differences in communication style."

In addition, they propose the following eight strategies for improvements in care for women:

1. Coverage of recommended evidence-based therapies without barriers
2. Screening and treatment for cardiovascular risk factors for all by primary care providers

3. Culturally tailored health education, preconception counseling, weight loss, and nutritional counseling
4. Media campaigns that share health messages in a variety of languages
5. Better clinical trial enrollment of underrepresented populations
6. Mandatory sex, race, and ethnicity reporting of participant data in research
7. Better recruitment of underrepresented populations in medicine
8. Better recruitment and retention of women, especially those of underrepresented races and ethnicities, in cardiovascular research

Seeing Patients as Partners

"Cardiovascular disease prevention is so crucial to impact not only mortality, but also quality of life for our patients," Mieres said, noting that the "biggest gaps" in the realm of CVD prevention research relate to women as well as minority racial and ethnic groups.

Moreover, she highlighted, even with the work that has been done in the last two decades, death rates for women began to increase about 2 years ago, and "we were losing the momentum that we had gained." Coupled with the fact that an AHA survey showed that between 40-50% of cardiologists feel ill-equipped to truly assess cardiovascular disease in women, the time is ripe for more attention on this issue, Mieres said.

On top of hoping that clinicians and researchers find inspiration to improve their care of women through reading this statement, Mehta said she wants patients, too, to find it useful. "We know patients are becoming better advocates for their own health," she said. "And so we want to make sure that they are all aware of this document as well."

To better provide patient-centered care, Mieres said clinicians need to view patients as part of the healthcare team. "When you are coming up with a

treatment strategy, you are co-creating a treatment strategy that is going to be sustainable to prevent the catastrophic effects of cardiovascular disease," she said. This involves understanding a woman's complete risk, including family history of hypertension and pregnancy related complications, for example.

It's equally important to be clued into the nonbiological factors like living environment, job status, chronic stress exposure, depression, and literacy level, as these will also "determine how we co-create that treatment plan," she concluded. "It's really a rethinking of seeing all patients as partners to incorporate what matters to them and their lifestyle changes to really improve adherence to a medical treatment plan, but also to ultimately improve cardiovascular outcomes."

9. Impact of Age and Sex on Left Ventricular Remodeling in Patients With Aortic Regurgitation

Background

Current guidelines for aortic regurgitation (AR) recommend the same linear left ventricular (LV) dimension for intervention regardless of age and sex.

Objectives

The purpose of this study was to evaluate the impact of age and sex on the degree of LV remodeling and outcomes.

Methods

We included consecutive patients with severe AR who were serially monitored by echocardiogram between 2010 and 2016. The 2 main endpoints were as follows: 1) LV end-systolic volume indexed to body surface area (LVESVi) and LV end-diastolic volume indexed to body surface area; and 2) adverse events (AE). We

evaluated the longitudinal rate of LV remodeling and determined the association between LV volume and AE by age and sex.

Results

A total of 525 adult patients (26% women) with a median echocardiogram follow-up of 2.0 years (IQR: 1.0-3.6 years) were included. At baseline, older patients (age ≥60 years) had smaller LV volumes compared with younger patients (age <60 years), eg, the mean LVESVi was 27.3 mL/m^2 vs 32.3 mL/m^2, respectively. Similarly, women had smaller LV volumes compared with men (mean LVESVi was 23.3 mL/m^2 vs 32.4 mL/m^2). On serial evaluation, older patients and women maintained smaller LV volumes compared with younger patients and men, respectively. There were 210 (40%) AE during follow-up. The optimal discriminatory threshold for AE varies by age and sex, eg, the LVESVi threshold was highest for young men (50 mL/m^2), intermediate for older men (35 mL/m^2), and lowest for women (27 mL/m^2).

Conclusions

On serial evaluation, older patients and women with chronic AR maintained smaller LV volumes than younger patients and men, respectively, and develop AE at lower LV volumes.

10. Aspirin Discontinuation at 24 to 28 Weeks' Gestation in Pregnancies at High Risk of Preterm Preeclampsia

IMPORTANCE

Aspirin reduces the incidence of preterm preeclampsia by 62% in pregnant individuals at high risk of preeclampsia. However, aspirin might be associated with an increased risk of peripartum bleeding, which could be mitigated by discontinuing aspirin before term (37 weeks of gestation) and by an accurate

selection of individuals at higher risk of preeclampsia in the first trimester of pregnancy.

OBJECTIVE

To determine whether aspirin discontinuation in pregnant individuals with normal soluble fms-like tyrosine kinase-1 to placental growth factor (sFlt-1:PlGF) ratio between 24 and 28 weeks of gestation was noninferior to aspirin continuation to prevent preterm preeclampsia.

DESIGN, SETTING, AND PARTICIPANTS

Multicenter, open-label, randomized, phase 3, noninferiority trial conducted in 9 maternity hospitals across Spain. Pregnant individuals (n = 968) at high risk of preeclampsia during the first-trimester screening and an sFlt-1:PlGF ratio of 38 or less at 24 to 28 weeks of gestation were recruited between August 20, 2019, and September 15, 2021; of those, 936 were analyzed (intervention: n = 473; control: n = 463). Follow-up was until delivery for all participants.

INTERVENTIONS

Enrolled patients were randomly assigned in a 1:1 ratio to aspirin discontinuation (intervention group) or aspirin continuation until 36 weeks of gestation (control group).

MAIN OUTCOMES AND MEASURES

Noninferiority was met if the higher 95% CI for the difference in preterm preeclampsia incidences between groups was less than 1.9%.

RESULTS

Among the 936 participants, the mean (SD) age was 32.4 (5.8) years; 3.4% were Black and 93% were White. The incidence of preterm preeclampsia was 1.48% (7/473) in the intervention group and 1.73% (8/463) in the control group (absolute difference, -0.25% [95% CI, -1.86% to 1.36%]), indicating noninferiority.

CONCLUSIONS AND RELEVANCE

Aspirin discontinuation at 24 to 28 weeks of gestation was noninferior to aspirin continuation for preventing preterm preeclampsia in pregnant individuals at high risk of preeclampsia and a normal sFlt-1:PlGF ratio.

11. Scheduled Childbirth Could Prevent At-Term Preeclampsia

A risk-stratified screening approach at 35 to 36 weeks of gestation can prevent at-term preeclampsia (cases that occur during weeks 37 to 42) , according to a study published online April 10 in Hypertension.

Laura A. Magee, M.D., from King's College Hospital in London, and colleagues aimed to identify optimal preeclampsia screening and timing of birth strategy for preeclampsia prevention. Preeclampsia screening was conducted at routine visits at 11 to 13 weeks of gestation (57,131 pregnancies screened; 1,138 term preeclampsia developed) or at 35 to 36 weeks of gestation (29,035 pregnancies screened; 619 term preeclampsia) with preeclampsia risks determined by U.K. National Institute for Health and Care Excellence guidance and the Fetal Medicine Foundation competing-risks model. The timing of birth for term preeclampsia prevention was assessed at fixed gestational time points (37, 38, 39, and 40 weeks) or dependent on preeclampsia risk based on the competing-risks model at 35 to 36 weeks.

The researchers found that compared with screening at 11 to 13 weeks, the proportion of term preeclampsia prevented was the highest and the number-needed-to-deliver was the lowest for preeclampsia screening at 35 to 36 weeks. Fewer cases of preeclampsia were prevented for National Institute for Health and Care Excellence than the competing-risks model for delivery at 37 weeks (28.8 versus 59.8 percent), and the number-needed-to-deliver was higher (16.4 versus 6.9, respectively). Similar preeclampsia prevention and number-needed-to-deliver were seen with the risk-stratified approach (by 57.2 percent and 8.4,

respectively) but would result in fewer women being induced at 37 weeks (1.2 versus 8.8 percent).

"Our findings suggest that over half of the cases of at-term preeclampsia may be prevented by timed (planned) birth," Magee said in a statement.

Reagents and relevant equipment were provided free of charge by several companies.

12. Third-Trimester Preeclampsia Screening Still Worthwhile, Data Suggest

It's worth screening women for preeclampsia risk in the third trimester when they're 35 to 36 weeks pregnant, not just earlier in the pregnancy, to assess who might still be vulnerable to developing the condition thereafter, a new observational analysis suggests.

Such patients might benefit from timed birth at 37 weeks to avoid preeclampsia, Laura A. Magee, MD (Addison House, Guy's Campus, London, England), note in their paper published yesterday in Hypertension. However, they say, this strategy of inducing labor requires further study in a randomized controlled trial.

"Term preeclampsia," occurring at 37 weeks and beyond, has unique aspects that set it apart from "preterm preeclampsia" that occurs beforehand, Magee explained to TCTMD.

"Preterm preeclampsia is sort of the 'poster child' that attracts the attention, because tiny babies and incubators and things, they're really emotive," she observed. "But about 75% of preeclampsia occurs at term gestational age, and importantly, the majority of the complications for moms and a substantial proportion of the complications for babies actually occur at term because of the sheer numbers of women and babies affected."

And while low-dose aspirin during pregnancy can reduce the risk of preterm cases, there's no known way to prevent term preeclampsia, Magee stressed. Even so, screening not just early but closer to delivery is a worthy pursuit, she added.

"No matter how accurate the mechanism is that you use in early pregnancy to identify women at increased risk, it doesn't accurately predict term disease," said Magee. "Like most prediction, you get better and better at it the closer you are to the event. . . . So you need to look at it at 35 to 36 weeks. Our perspective is that this is worth considering, because the majority of the preeclampsia is yet to come."

For pregnant women, the results of screening can help them and their partners to both mentally prepare and make informed decisions about what steps, if any, to take, she added.

There also are implications for a woman's health over her lifetime, as it's been well established that preeclampsia and gestational hypertension translate into higher CV risk many decades later.

"What we don't know is whether, if we prevent preeclampsia, we will decrease that cardiovascular risk. [It's unknown] how much is driven by underlying risk factors and how much may be direct damage related to the preeclampsia. There's far more evidence for the former than the latter, but it remains a theoretical possibility that prevention of that preeclampsia may be beneficial in and of itself," Magee commented.

Screening Tools and Timing of Birth

For their study, Magee and colleagues retrospectively analyzed data from two cohorts of pregnant women who gave birth to babies without major anomalies ≥ 24 weeks' gestation at two UK-based maternity hospitals. They used information gathered during routine visits to gauge preeclampsia risk with several screening tools: UK National Institute for Health and Care Excellence (NICE) guidance and

the Fetal Medicine Foundation (FMF) competing-risks model, as well as a model based on the latter that further stratified women into five risk categories.

The NICE guidance considers clinical factors like comorbidities, older age, family history, and higher body mass index, among other things. The FMF model also includes medical history and demographic information with the addition of metrics like mean arterial pressure, uterine artery pulsatility index, and serum concentration of placental growth factor (PIGF) or, alternatively, serum concentration of pregnancy-associated plasma protein-A (PAPP-A).

What we don't know is whether, if we prevent preeclampsia, we will decrease that cardiovascular risk. Laura A. Magee

At 11-13 weeks' gestation, 57,131 women were screened using these tools and among them 1,138 (2%) developed preeclampsia at 37 weeks or later. During routine visits at 35-36 week's gestation, 29,035 women were screened and 619 (2.1%) developed preeclampsia at 37 weeks or later.

Pregnancy outcomes were similar between these two groups, as were most patient characteristics. Women delivered at 40 weeks on average, about two-thirds had spontaneous onset of labor, and one-quarter gave birth via cesarean section.

Although the various screening tools performed slightly differently, researchers found that using them at 35-36 weeks, as opposed to at 11-13 weeks, prevented a greater proportion of term preeclampsia. The later screening time also had the lowest number of induced deliveries required to prevent one case of term preeclampsia.

Use of the FMF competing-risks model at 35-36 weeks was better at identifying women who could benefit from timed birth at 37 weeks than the NICE guidance, with the intervention reducing preeclampsia cases by 59.8% (vs 28.8%) and having a lower the number-needed-to-deliver (6.9 vs 16.4). Applying risk

stratification to that model allowed similar preeclampsia prevention (57.2%) and a similar number-needed-to-deliver (8.4), and in the process required fewer women to have timed birth at 37 weeks. NICE guidance based on clinical factors alone was a less-effective screening tool.

Magee said that some clinicians are already screening their pregnant patients at 35-36 weeks, though it's an uncommon practice.

But exactly what's to be done with that information gleaned from screening hasn't yet been established, she noted. "These are observational data. They are suggestive that this is a strategy that may be highly effective, particularly [when] risk is personalized. So, women who are at very high risk, like at least a 50% risk of developing preeclampsia at term, are recommended for timed initiation of birth at 37 weeks," especially since they have a higher risk of going into spontaneous labor ahead of the expected delivery date.

Others might be better suited to timed birth at 38 weeks based on their risk level—the idea is to target those most likely to benefit while minimizing the potential for harm, Magee continued. "Of course the risk of developing preeclampsia at term is rising as gestation goes on. And the risk of newborn health problems from being born closer to 37 weeks as opposed to farther away is going down just based on maturity. So any timed birth is a balance of those two things."

Importantly, "timed birth by labor induction is an intervention that can be offered around the world. You don't need expensive medications: labor can be induced by a mechanical means with [for example] a Foley catheter, and it's highly effective," she emphasized.

Thus, the researchers point out, the strategy might be particularly useful in regions where the capacity to care for women with preeclampsia is limited. These under-resourced settings are "where the vast majority of women with

preeclampsia die, and where timed birth can be offered easily and inexpensively," they observe. Even in high-income countries, there are rural areas where access to care could be a challenge, Magee noted to TCTMD.

As for next steps, the Fetal Medicine Foundation is funding a trial that's soon set to begin and will look at the best timing of birth to prevent preeclampsia, she said.

13. A Call to Action For Black Maternal Health Week

Black women in the U.S. are three times more likely to die from pregnancy-related death than White women.[1] This staggering statistic highlights the urgent need to address the multifactorial causes for disparities in maternal health outcomes.

While Black women are more likely to have underlying risk factors including diabetes, hypertension and chronic kidney disease, these alone do not entirely explain the disparities, but rather reflect broader systemic issues. Social determinants of health (SDOH), such as insurance status compounded by state-to-state variation in Medicaid expansion and laws regulating reproductive health, along with poverty, housing instability, poor access to food as well as implicit bias, discrimination, structural racism and a lack of diversity in the health care workforce, all contribute to these striking, disparate outcomes.[2] It is crucial to recognize and address these systemic issues to ensure equitable access to quality maternal health care for all women, regardless of race or ethnicity.

Many vulnerable populations are often overlooked when discussing Black maternal health. This includes veterans, active military, persons living in rural communities or low-income neighborhoods, pregnant women with substance use or psychiatric disorders and incarcerated individuals. These vulnerable groups require particularly concerted efforts to improve their access to equitable maternal health care.[3]

The recent Dobbs v. Jackson Women's Health Organization Supreme Court decision threatens access to reproductive health care, particularly for Black women.[4] This decision highlights the importance of legislative action to drive change. The Momnibus of 2021 and the Helping MOMs Act are two pieces of legislation that aim to address the maternal mortality crisis in the U.S. by addressing SDOH including insurance coverage. The Consolidated Appropriations Act of 2023 provides funding for essential programs such as rural broadband; rural housing loans and rental assistance; Women, Infants and Children (WIC); Supplemental Nutrition Assistance Program (SNAP); child nutrition programs; Centers for Disease Control and Prevention funding for safe motherhood and infant health; and the Substance Abuse Mental Health Services Administration (SAMHSA).

Despite the legislative actions that have been taken, there is still much work to be done to address the maternal mortality crisis in the U.S. A paradigm shift in the approach to maternal health care is required, ensuring all mothers have maternal health access from preconception through postpartum. New models of postpartum care are needed to ensure that Black women receive the care they need beyond the delivery period, which is often a time of increased risk of morbidity and mortality. This will also serve as a window of opportunity for risk assessment to prevent future cardiovascular disease. These changes will require a transformation in provider payment systems with incentivization of quality and equitable care as well as promotion of value-based care.[5]

It is also essential to recognize the diversity of Black women when proposing solutions and tailoring health care to meet their unique needs. Education and awareness are critical components of addressing the maternal mortality crisis. Health care providers and policymakers must be educated on implicit bias, basic cardio-obstetric care, and inclusive representation within the health care workforce and research.[6]

Addressing the disparities in maternal health outcomes for Black women in the U.S. requires a comprehensive approach that takes into account the complex interplay of SDOH, implicit bias, discrimination and structural racism. By recognizing and addressing these systemic issues, we can work towards ensuring equitable access to quality maternal health care for all women, regardless of their race or ethnicity, including vulnerable populations.

Black Maternal Health Week is an opportunity to raise awareness about the alarming disparities in maternal mortality rates among Black women in the U.S., and amplify efforts for research, policy changes and solutions to advance health equity.

14. Unravelling associations between maternal health and congenital heart defect risk in the offspring—the FINNPEDHEART study

Congenital heart defects (CHDs) are structural malformations of the heart and intrathoracic vessels. CHDs are the most common congenital malformations in children, affecting roughly one in a hundred new-borns. The care of CHD patients is resource intensive. CHDs accounted for 3.7% of all paediatric hospitalizations in the US in 2009, and the costs of these were estimated at $5.6 billion, representing 15.1% of costs for all paediatric hospitalizations.1 Given that even less complex CHD are associated with significant mortality and morbidity, and a shorter life-expectancy,2,3 primary prevention of CHD with significant benefit to public health should be the essential goal. The FINNPEDHEART project utilizes Finnish nationwide registers, biobank, and genomic data to identify modifiable maternal factors predisposing for offspring's CHD, ultimately aiming to reduce the incidence of CHD.

Both genes and environmental factors, such as maternal diabetes and obesity,4 contribute to the pathogenesis of CHD (Figure 1). Offspring's risk for CHD is 5%–10% if a parent has a CHD, and for unknown reasons, CHD is inherited more

often from the mother than the father.5 Due to the complex inheritance pattern, reduced penetrance, and variable expressivity, identifying gene variants associated with CHD has been challenging. Indeed, relatively few causal genes have been identified. It seems likely that single gene disorders cause the minority of isolated CHD and most isolated CHD are multifactorial, ie. oligogenic or caused by environmental factors in genetically susceptible individuals. The genetic susceptibility has been demonstrated in a number of genome-wide association studies (GWAS), where genome-wide significant loci for certain CHD subgroups and for CHD in general have been identified .6

Little is known about the molecular and cellular-level events that lead to abnormal cardiac development in CHD pregnancies. In addition, the pathophysiological mechanisms caused by maternal chronic conditions leading to CHD are poorly known. Interestingly, CHD and adult cardiovascular disease share common risk factors, such as obesity, diabetes mellitus, and pre-eclampsia.7,8 However, this link has received relatively little attention in CHD research. Recent studies suggest early cardiovascular morbidity in mothers of infants with CHD 7 and adults with lower complexity CHD2 and raise the question: Could cardiac development and adulthood cardiovascular morbidity share similar genetic mechanisms? Deeper understanding of the risk factors for CHD and cardiovascular disease early in life, as well as association between these has the potential to reduce the burden of both diseases. The FINNPEDHEART study approaches the knowledge gap in CHD aetiology from the maternal side and hypotheses the existence of an aetiologically distinct 'environmental CHD' subgroup, where in addition to the child's genes, maternal genetics and gene expression plays a major role in disease development.

Finland provides exceptional conditions for epidemiologic and genetic research due to its universal tax-funded health care system, large-scale biobanks, and population-based nationwide registers. First, several Finnish registers record phenotypes and health events over the entire lifespan, including the Medical Birth Register, Register of Congenital Malformations, Care Register for Health

Care, Causes of Death Register, the National Infectious Diseases Register, Cancer Register, Primary Health Care Register, and Medication Reimbursement Register. Importantly, all citizens have personal identity numbers, enabling individual-level linkage of these registries. Second, Finnish municipalities organize, provide and finance primary, secondary and tertiary care, and as a part of this system free maternity care, which 99.5% of expectant mothers utilize.9 As a part of the maternity follow-up, certain viral antibodies have been screened from a blood sample between 10 and 14 weeks of gestation since 1983. The leftover samples from 1983–2016 have been deposited in the biobanks for research purposes. Sera exists from ~98% of pregnancies, comprising more than 2 million samples. Finally, the FinnGen Project is a large-scale biobank study that aims to genotype 500 000 Finnish participants recruited from hospitals as well as from prospective and retrospective epidemiological and disease-based cohorts. The FinnGen genotype data are combined with longitudinal register data and then provided for research for multiple purposes, for example to identify genetic determinants of disease.

The FINNPEDHEART project will utilize these unique data collections to study the maternal origins of offspring's CHD. Three different approaches (Figure 2) will be used: (i) Finnish national registers gathering health related information of all Finns from birth to death will be used in a cohort of ~1.5 million children, and their 1 million unique mothers and fathers to determine and compare cardiovascular illness, such as metabolic conditions, atherosclerosis and related traits, between parents who have offspring with CHD and unaffected control parents. (ii) Genotype data from the FinnGen project will be utilized to identify maternal genetic risk loci for offspring's CHD, and (iii) Maternal first trimester serum samples from pregnancies with and without CHD will be analysed to identify CHD associated biomarkers.

The FINNPEDHEART approach of observing environmental CHD with a maternal genetic risk profile as its own subtype will provide novel information on how the combination of maternal genetic and environmental risk factors can contribute to CHD development during early pregnancy. The study questions are timely, since maternal obesity has been increasing at an alarming rate during recent years and cardiovascular morbidity is the leading cause of death in women worldwide accounting for 9% of deaths in 20–44-year-old women in the United States in 2018. In European countries, 7–25% of expectant mothers are overweight, and in the United States only 45% of mothers have a normal weight when entering pregnancy.4

Recognising modifiable risk factors for offspring's CHD and understanding the risk transmission from the mother to the foetus can aid in developing guidelines and treatments to reduce the incidence of these defects. Lifestyle factors such as dietary habits, body composition, and physical activity, as well as certain dietary supplements and optimal treatment of chronic conditions represent targets for preconception and prenatal interventions. For example, maternal early pregnancy serum lipid profile could be optimized.10 Moreover, by identifying risk factors for offspring's CHD, more intense monitoring of pregnancy could be targeted to those with the highest risk. Finally, identifying maternal early pregnancy biomarkers and maternal genetic loci associated with offspring's CHD will provide new, critically needed insights for future research on the cellular and molecular mechanisms of cardiac development.

15. Risk and trajectory of premature ischaemic cardiovascular disease in women with a history of pre-eclampsia: a nationwide register-based study

Aims

Pre-eclampsia increases women's lifetime risk of cardiovascular disease (CVD). Little is known about the trajectory of CVD after pre-eclampsia, limiting the

usefulness of this knowledge for informing screening, prevention, and interventions. We investigated when the risk of CVD increases after pre-eclampsia and how the risk changes over time since pregnancy.

Methods and results

This register-based study included 1 157 666 women with >1 pregnancy between 1978 and 2017. Cumulative incidences of acute myocardial infarction (AMI) and ischaemic stroke were estimated, as well as hazard ratios (HRs) by attained age and time since delivery. Up to 2% [95% confidence interval (CI): 1.46–2.82%] of women with pre-eclampsia in their first pregnancy had an AMI or stroke within two decades of delivery, compared with up to 1.2% (95% CI: 1.08–1.30%) of pre-eclampsia-free women; differences in cumulative incidences were evident 7 years after delivery. Ten years after delivery, women with pre-eclampsia had four- and three-fold higher rates of AMI (HR = 4.16, 95% CI: 3.16–5.49) and stroke (HR = 2.59, 95% CI 2.04–3.28) than women without pre-eclampsia; rates remained doubled >20 years later. Women with pre-eclampsia aged 30–39 years had five-fold and three-fold higher rates of AMI (HR = 4.88, 95% CI 3.55–6.71) and stroke (HR = 2.56, 95% CI 1.95–3.36) than women of similar age without pre-eclampsia.

Conclusions

Women with a history of pre-eclampsia have high rates of AMI and stroke at early ages and within a decade after delivery. The findings suggest that pre-eclampsia history could be useful in identifying women at increased risk of CVD and that targeted interventions should be initiated soon after delivery.

16. **Cardiovascular risk profile after a complicated pregnancy across ethnic groups: the HELIUS studyAims**

Aims

Little is known about how pregnancy complications and cardiovascular disease (CVD) risk are associated, specifically among ethnic minorities. In this study, we examined this association in women from six ethnic groups, and the potential value of pregnancy complications as eligibility criterion for CVD risk screening.

Methods and results

We conducted a cross-sectional study combining obstetric history from the Dutch perinatal registry with data on cardiovascular risk up to 15 years after pregnancy from the multi-ethnic HELIUS study. We included 2466 parous women of Dutch, South-Asian Surinamese, African Surinamese, Ghanaian, Turkish, and Moroccan origin. Associations were studied across ethnicities and predictive value of pregnancy complications for CVD risk factors above traditional eligibility criteria for CVD risk screening was assessed using Poisson regression. History of hypertensive disorders of pregnancy and preterm birth were associated with higher prevalence of chronic hypertension and chronic kidney disease across most groups [prevalence ratio (PR): 1.6–1.9]. Gestational diabetes mellitus was associated with increased type 2 diabetes mellitus risk, particularly in ethnic minority groups (PR: 4.5–7.7). Associations did not significantly differ across ethnic groups. The prediction models did not improve substantially after adding pregnancy complications to traditional eligibility criteria for CVD risk screening.

Conclusion

History of hypertensive disorders of pregnancy, preterm birth, and gestational diabetes mellitus is associated with CVD risk factors in parous women, without evidence of a differential association across ethnic groups. However, addition of pregnancy complications to traditional eligibility criteria for CVD risk screening does not substantially improve the prediction of prevalent CVD risk factors.

17. Primary prevention of cardiovascular disease and complications in pregnancy, detect individual risk, and start early!

This official statement of the American Heart Association (AHA) in 2020 represents the urgent call for action focusing pregnant women with respect to their individual cardiovascular (CV) risk, as CVD is a major cause of pregnancy related mortality.

Detailed scientific guidelines addressing the management of specific pregnancy complications as well as CVDs accompanying pregnancy are available, and it is far beyond the scope of this short clinical comment to fully encompass this important and challenging field.[2,3] Instead, animated by the actually published results of the HELIUS study, the present comment confines to discuss the clinical potential of timely activities for primary CVD prevention in women before pregnancy is anticipated.[4]

Aiming a better understanding of the interaction between CV risk profiles and pregnancy complications among ethnic minorities, Burger et al. conducted a cross-sectional data-linkage study combining obstetric histories from the Dutch perinatal registry (Perined) with CV risk profiles up to 15 years after pregnancy out of the data pool of the multi-ethnic HELIUS study.[4–6] In total, 2466 parous women of six different ethnicities out of Europe, Asia, and Africa were included. The key results were as follows:

- Hypertension disorders of pregnancy (HDP) and preterm birth were associated with an increased prevalence of chronic hypertension and chronic kidney disease in most groups, and gestational diabetes was associated with an increased prevalence of type 2 diabetes especially in ethnic minority groups.
- While the addition of pregnancy complications to well-accepted CVD risk factors and risk diseases did not substantially improve traditional 'CVD

risk prediction models', ethnic disparities in post pregnancy CV risk estimations were confirmed. 7

The authors conclude that these data support the hypothesis of common pathophysiological mechanisms and pathways being involved in both, the development of CVD and—at least in part—the facilitation of pregnancy complications.

Indeed, growing evidence supports pre-existing CVD being a strong risk factor for the development of pre-eclampsia. Impaired maternal CV performance may directly lead to utero-placental hypo-perfusion, thereby contributing to secondary placental dysfunction in pre-eclampsia.8 Finally, the presence of shared risk factors for CVD and pre-eclampsia support the pathophysiological role of pre-existing CVD in the development of later HDP.9 These shared risk factors include age, obesity, diabetes, hypertension, renal disease, hyperlipidaemia, and family history of CVD or pre-eclampsia.2,8–10

Endothelial dysfunction, an early pathophysiological consequence of many CV risk factors and risk diseases, represents one of the crucial mechanisms leading to disturbance of organ perfusion, thereby inducing organ dysfunction and promoting the development of atherosclerosis. Endothelial dysfunction also is known to be involved in the complex pathophysiology of preeclampsia.10

If pregnancy complications are at least in part the result of common pathophysiological key mechanisms promoting organ hypo-perfusion and atherosclerosis (keeping in mind additional, concomitant mechanisms like genetic predisposition and pathological immune responses),11 an early start and a rigorous realization of primary CV prevention timely before pregnancy are warranted.12 Primary prevention in the preconception period thereby includes the early assessment of the individual CV risk profile (life style, CV risk diseases, CVD) being followed by strong efforts to consequently reduce this individual CV risk to the benefit of mother, foetus, and newborn.12

If we assume about 4 million deliveries within the European Union in 2020, we may calculate with 200 000–400 000 (5–10%) pregnancy-related hypertensive disorders per year.[2,13] Actually, it is well accepted that hypertensive disorders of pregnancy must entail a structured clinical evaluation of the individual CV risk being followed by targeted therapeutic interventions.[14–17] However, keeping in mind the potentially deleterious outcomes of high risk pregnancies themselves, every effort should be made to effectively establish primary prevention of CVDs in beforehand of anticipated pregnancies and thereby markedly increase safety of pregnant women, foetus, and newborn! It has sometimes been announced that pregnancy may be the 'nature`s stress test' for heart and life.[15,18] However, neither the baby nor the mother should be exposed to preventable 'stress tests' that include a significantly increased risk for both!

Therefore, these aspects not only need to be discussed by medical guidelines on obstetrics but also should be addressed in more detail and with more emphasis in general clinical guidelines of CVD prevention, thereby supporting increased knowledge and optimized care for a successful and healthy pregnancy and delivery.[19] Indeed, following the AHA statement cited above, pregnancy complications and their prevention should belong to the core curriculum not only for gynaecologists and obstetricians but also for family doctors and especially for cardiologists.[1]

18. Overcoming professional barriers encountered by women in interventional cardiology: an EAPCI statement

Despite the increasing proportion of female medical and nursing students, there is still a significant under-representation of women working as healthcare providers in interventional cardiology, with very few of them reaching senior leadership, academic positions, or acting principal investigators, as well as actively involved in company advisory boards. In this position paper, we will

describe the current status of women working in interventional cardiology across Europe. We will also provide an overview of the most relevant determinants of the under-representation of women at each stage of the interventional cardiology career path and offer practical suggestions for overcoming these challenges.

19. **U-shaped relationship between apolipoprotein A1 levels and mortality risk in men and women**

Background

Apolipoprotein A1 (ApoA1) is the principal protein component of high-density lipoprotein (HDL). Although low HDL cholesterol (HDL-C) levels are known to be associated with greater cardiovascular risk, recent studies have also shown heightened mortality risk at very high HDL-C levels.

Aims

To investigate the sex-specific association between elevated ApoA1 levels and adverse outcomes, and their genetic basis.

Methods

A prospective cohort study of United Kingdom Biobank participants without coronary artery disease at enrollment was performed. The primary exposure was serum ApoA1 levels. The primary and secondary outcome measures were cardiovascular and all-cause death, respectively.

Results

In 402 783 participants followed for a median of 12.1 years, there was a U-shaped relationship between ApoA1 levels and both cardiovascular as well as all-cause mortality, after adjustment for traditional cardiovascular risk factors. Individuals in the highest decile of ApoA1 levels (1.91–2.50 g/L) demonstrated higher cardiovascular (HR 1.21, 95% CI 1.07–1.37, $P < 0.0022$) and all-cause mortality (HR 1.14, 95% CI 1.07–1.21, $P < 0.0001$) compared with those within the lowest risk eighth decile (1.67–1.75 g/L). The U-shaped relationship was present in both sexes, though more pronounced in men. Sensitivity analyses showed that cardiovascular mortality rates were higher in those with greater alcohol intake ($P < 0.004$). Adjustment for polygenic variation associated with

higher ApoA1 levels did not attenuate the effect of very high ApoA1 levels on mortality. In the sub-group with very elevated HDL-C levels (> 80 mg/dL in men, > 100 mg/dL in women), there was no association between ApoA1 levels and mortality.

Conclusion

Both very low and very elevated ApoA1 levels are associated with higher cardiovascular and all-cause mortality.

20. Later Risks Noted After BSO With Hysterectomy in Peri/Premenopausal Women

For women undergoing hysterectomy for benign conditions, bilateral salpingo-oophorectomy (BSO) is associated with an increased risk for adverse outcomes, according to a study published online April 18 in the Annals of Internal Medicine.

Mathilde Gottschau, M.D., Ph.D., from the Danish Cancer Society Research Centre in Copenhagen, and colleagues compared long-term outcomes in women aged 20 years and older with and without BSO during hysterectomy for benign conditions using data from a population-based cohort. Data were included for 142,985 women with hysterectomy for a benign condition: 22,974 and 120,011 with and without BSO, respectively.

The researchers found that women with BSO who were younger than 45 years at surgery had a higher 10-year cumulative risk for hospitalization for cardiovascular disease than those without BSO (risk difference [RD], 1.19 percentage points). At ages 45 to 54, 55 to 64, and 65 years or older, women with BSO had a higher 10-year cumulative risk for cancer (RDs, 0.73, 1.92, and 2.54 percentage points, respectively). In all age groups, women with BSO had higher 10-year mortality, although the differences were significant for ages 45 to 54 years only (RD, 0.79 percentage points). For women aged 65 years and older, mortality at 20 years was inconsistent with that at 10 years.

"The lack of a clear survival benefit and the cancer excess in postmenopausal women suggest the need for a cautious approach when deciding whether to perform BSO at hysterectomy in these women," the authors write.

21. Prenatal Smoking Linked to Less Childhood T1D Risk

KEY TAKEAWAYS

- IN A NATIONWIDE SWEDISH STUDY OF MORE THAN 3 MILLION PEOPLE, PRENATAL EXPOSURE TO SMOKING WAS SIGNIFICANTLY ASSOCIATED WITH A REDUCED RISK FOR DEVELOPING TYPE 1 DIABETES DURING CHILDHOOD, BUT NOT AFTER THE OFFSPRING TURNED 25 YEARS OLD.
- YOUNG ADULTS WHO SMOKED DID NOT HAVE A REDUCED RISK FOR DEVELOPING TYPE 1 DIABETES, AND THE EVIDENCE SHOWED A SIGNAL THAT THE RISK FOR ADULT-ONSET TYPE 1 DIABETES MAY HAVE INCREASED IN THIS GROUP.

WHY THIS MATTERS

- PRENATAL EXPOSURE TO SMOKING HAS PREVIOUSLY BEEN LINKED TO A REDUCED RISK OF TYPE 1 DIABETES IN CHILDREN COMPARED WITH THOSE WITH NONSMOKING MOTHERS, BUT NO PRIOR REPORTS HAVE ADDRESSED WHETHER THIS PROTECTION CONTINUES INTO ADULTHOOD OR APPLIES TO ADULTS WHO THEMSELVES SMOKE.
- THIS IS THE FIRST STUDY TO INVESTIGATE MATERNAL SMOKING DURING PREGNANCY IN RELATION TO TYPE 1 DIABETES INCIDENCE IN OFFSPRING BEYOND CHILDHOOD.
- THE AUTHORS CAUTIONED THAT THE CLINICAL SIGNIFICANCE OF THEIR FINDINGS WAS "DIFFICULT TO SEE" CONSIDERING THE MANY

ADVERSE EFFECTS FROM SMOKING DURING PREGNANCY. THEY INSTEAD HIGHLIGHTED THAT THEIR FINDINGS ADD TO UNDERSTANDING THE ETIOLOGY OF TYPE 1 DIABETES.

STUDY DESIGN

- THE STUDY USED DATA COLLECTED BY SWEDISH NATIONAL REGISTRIES FOR 3,176,072 PEOPLE BORN FROM 1983 TO 2014, AND ON ALL 1,209,618 WOMEN WHO GAVE BIRTH TO A CHILD DURING THIS PERIOD AND HAD INFORMATION RECORDED ON THEIR SMOKING HISTORY DURING PREGNANCY. THE BIRTH COHORT INCLUDED 18,789 PEOPLE WITH INCIDENT TYPE 1 DIABETES BEFORE THEY WERE 31 YEARS OLD, INCLUDING 16,275 PEOPLE WHO DEVELOPED TYPE 1 DIABETES BY THE TIME THEY WERE 18 YEARS OLD.
- A SECOND ANALYSIS FOCUSED ON INCIDENT DIABETES AND ADULT SMOKING AMONG 1,608,291 PEOPLE 19 TO 30 YEARS OLD AND FOLLOWED UNTIL AGE 30 OR THE YEAR 2019, OF WHOM 1274 DEVELOPED TYPE 1 DIABETES.

KEY RESULTS

- MATERNAL SMOKING DURING PREGNANCY WAS SIGNIFICANTLY ASSOCIATED WITH A LOWER INCIDENCE OF TYPE 1 DIABETES IN CHILDREN 0 TO 18 YEARS OLD COMPARED WITH CHILDREN BORN TO NONSMOKING MOTHERS, WITH A HAZARD RATIO OF 0.76. FOR OFFSPRING 19 TO 30 YEARS OLD, THE HAZARD RATIO FOR INCIDENT TYPE 1 DIABETES WAS ALSO SIGNIFICANT, 0.88.
- THE ANALYSIS SHOWED NO DOSE-RESPONSE RELATIONSHIP BETWEEN THE AMOUNT OF MATERNAL SMOKING AND DIABETES INCIDENCE IN THE OFFSPRING, AND ADJUSTMENT FOR BODY WEIGHT INDEX AND SMOKING BY THE OFFSPRING THEMSELVES HAD NO EFFECT ON THE OBSERVED ASSOCIATIONS.

- THE DATA SHOWED A 22% TO 29% LOWER INCIDENCE OF TYPE 1 DIABETES IN THE OFFSPRING OF SMOKING VS NONSMOKING MOTHERS UNTIL THEY WERE 24 YEARS OLD, BUT NO DIFFERENCE EXISTED AMONG OFFSPRING WHO WERE 25 TO 30 YEARS OLD.
- A PERSONAL HISTORY OF SMOKING WAS SIGNIFICANTLY ASSOCIATED WITH INCIDENT TYPE 1 DIABETES IN PEOPLE WITH A FAMILY HISTORY OF DIABETES WITH A SIGNIFICANT HAZARD RATIO OF 1.34, BUT NO SIGNIFICANT ASSOCIATION EXISTED FOR THOSE WITHOUT THIS FAMILY HISTORY.

LIMITATIONS

- THE STUDY RELIED ON SELF-REPORTED SMOKING BEHAVIOR, WHICH MAY HAVE ESPECIALLY UNDERESTIMATED MATERNAL SMOKING DURING PREGNANCY.
- THE STUDY LACKED INFORMATION ON PATERNAL SMOKING DURING PREGNANCY OR CHILDHOOD.
- THE STUDY USED AN EXCLUSIVELY SWEDISH POPULATION, SO GENERALIZABILITY TO OTHER POPULATIONS IS NOT CLEAR.

22. **Cardiac Arrest During Delivery Hospitalization**

BACKGROUND

Estimates of cardiac arrest occurring during delivery guide evidence-based strategies to reduce pregnancy-related death.

OBJECTIVE

To investigate rate of, maternal characteristics associated with, and survival after cardiac arrest during delivery hospitalization.

DESIGN

Retrospective cohort study.

SETTING

U.S. acute care hospitals, 2017 to 2019.

PARTICIPANTS

Delivery hospitalizations among women aged 12 to 55 years included in the National Inpatient Sample database.

MEASUREMENTS

Delivery hospitalizations, cardiac arrest, underlying medical conditions, obstetric outcomes, and severe maternal complications were identified using codes from the International Classification of Diseases, 10th Revision, Clinical Modification. Survival to hospital discharge was based on discharge disposition.

RESULTS

Among 10 921 784 U.S. delivery hospitalizations, the cardiac arrest rate was 13.4 per 100 000. Of the 1465 patients who had cardiac arrest, 68.6% (95% CI, 63.2% to 74.0%) survived to hospital discharge. Cardiac arrest was more common among patients who were older, were non-Hispanic Black, had Medicare or Medicaid, or had underlying medical conditions. Acute respiratory distress syndrome was the most common co-occurring diagnosis (56.0% [CI, 50.2% to 61.7%]). Among co-occurring procedures or interventions examined, mechanical ventilation was the most common (53.2% [CI, 47.5% to 59.0%]). The rate of survival to hospital discharge after cardiac arrest was lower with co-occurring disseminated intravascular coagulation (DIC) without or with transfusion (50.0% [CI, 35.8% to 64.2%] or 54.3% [CI, 39.2% to 69.5%], respectively).

LIMITATIONS

Cardiac arrests occurring outside delivery hospitalizations were not included. The temporality of arrest relative to the delivery or other maternal complications is unknown. Data do not distinguish cause of cardiac arrest, such as pregnancy-related complications or other underlying causes among pregnant women.

CONCLUSION

Cardiac arrest was observed in approximately 1 in 9000 delivery hospitalizations, among which nearly 7 in 10 women survived to hospital discharge. Survival was lowest during hospitalizations with co-occurring DIC.

23. Risk for New CVD Increased for Those With Prenatal Depression

Individuals with prenatal depression have an increased risk for a new cardiovascular disease (CVD) diagnosis, according to a study published online April 19 in the Journal of the American Heart Association.

Christina M. Ackerman-Banks, M.D., from the Yale University School of Medicine in New Haven, Connecticut, and colleagues conducted a longitudinal population-based study involving pregnant persons with deliveries during 2007 to 2019 to estimate the cumulative risk for new CVD in the first 24 months postpartum among those diagnosed with prenatal depression versus those without depression diagnosed during pregnancy. Data were included for 119,422 pregnancies.

The researchers found that the risks for ischemic heart disease, arrhythmia/cardiac arrest, cardiomyopathy, and new hypertension were increased in association with prenatal depression (adjusted hazard ratios, 1.83, 1.60, 1.61, and 1.32, respectively). Several of these associations persisted when the analyses were stratified by co-occurring hypertensive disorders of pregnancy.

"Complications during pregnancy, including prenatal depression, impact long-term cardiovascular health," Ackerman-Banks said in a statement. "The

postpartum period provides an opportunity to counsel and screen people for cardiovascular disease in order to prevent these outcomes."

24. **How much does hypertension in pregnancy affect the risk of future cardiovascular events?**

Hypertensive disorders in pregnancy (HDP) include essential (or secondary) hypertension occurring before 20 weeks of gestation or in women already on antihypertensive therapy prior to pregnancy, gestational hypertension, developing after 20 weeks of gestation without significant proteinuria, and pre-eclampsia or AH onset after 20 weeks of pregnancy in the presence of proteinuria. The development of HDP is associated with a higher incidence of long-term cardiovascular (CV) adverse events, such as myocardial infarction, heart failure, stroke, and CV death. Women who develop high blood pressure in their first pregnancy have an increased risk of complication in a subsequent pregnancy. In the years following delivery, pregnant women with hypertensive disorders develop subclinical atherosclerosis and alterations of cardiac structure and function that may lead to CV disease and heart failure. Thus, it is recommended to monitor these changes over time and subject in pregnant women with these characteristics to CV surveillance through structured and multidisciplinary interventions for CV prevention.

25. Cancer Treatment-Related Cardiovascular Toxicity in Gynecologic Malignancies: JACC: CardioOncology State-of-the-Art Review

Improvements in early detection and treatment of gynecologic malignancies have led to an increasing number of survivors who are at risk of long-term cardiac complications from cancer treatment. Multimodality therapies for gynecologic malignancies, including conventional chemotherapy, targeted therapeutics, and hormonal agents, place patients at risk of cancer therapy-related cardiovascular toxicity during and following treatment. Although the cardiotoxicity associated

with some female predominant cancers (eg, breast cancer) have been well recognized, there has been less recognition of the potential adverse cardiovascular effects of anticancer therapies used to treat gynecologic malignancies. In this review, the authors provide a comprehensive overview of the cancer therapeutic agents used in gynecologic malignancies, associated cardiovascular toxicities, risk factors for cardiotoxicity, cardiac imaging, and prevention strategies.

Highlights

- Cancer therapy is associated with CV toxicities in gynecologic cancers
- Risk stratification at baseline and management of CV risk factors/disease is key
- Prospective studies are needed on CV impact of cancer therapies in these patients

26. Sex- and age-specific normal values for automated quantitative pixel-wise myocardial perfusion cardiovascular magnetic resonance

Aims

Recently developed in-line automated cardiovascular magnetic resonance (CMR) myocardial perfusion mapping has been shown to be reproducible and comparable with positron emission tomography (PET), and can be easily integrated into clinical workflows. Bringing quantitative myocardial perfusion CMR into routine clinical care requires knowledge of sex- and age-specific normal values in order to define thresholds for disease detection. This study aimed to establish sex- and age-specific normal values for stress and rest CMR myocardial blood flow (MBF) in healthy volunteers.

Methods and results

A total of 151 healthy volunteers recruited from two centres underwent adenosine stress and rest myocardial perfusion CMR. In-line automatic reconstruction and post processing of perfusion data were implemented within the Gadgetron software framework, creating pixel-wise perfusion maps. Rest and stress MBF were measured, deriving myocardial perfusion reserve (MPR) and were subdivided by sex and age. Mean MBF in all subjects was 0.62 ± 0.13 mL/g/min at rest and 2.24 ± 0.53 mL/g/min during stress. Mean MPR was 3.74 ± 1.00. Compared with males, females had higher rest (0.69 ± 0.13 vs. 0.58 ± 0.12 mL/g/min, $P < 0.01$) and stress MBF (2.41 ± 0.47 vs. 2.13 ± 0.54 mL/g/min, $P = 0.001$). Stress MBF and MPR showed significant negative correlations with increasing age ($r = -0.43$, $P < 0.001$ and $r = -0.34$, $P < 0.001$, respectively).

Conclusion

Fully automated in-line CMR myocardial perfusion mapping produces similar normal values to the published CMR and PET literature. There is a significant increase in rest and stress MBF, but not MPR, in females and a reduction of stress MBF and MPR with advancing age, advocating the use of sex- and age-specific reference ranges for diagnostic use.

27. Takotsubo syndrome: more frequent in women, more dangerous in men

Takotsubo syndrome (TTS) is an acute myocardial disease characterized by reversible left ventricular dysfunction, in the absence of obstructive coronary artery disease, caused by adrenergic overactivity and associated with non-negligible morbidity and mortality. Takotsubo syndrome, by far more frequent in women, who account for 9 out of 10 cases, is generally triggered by intense psychoemotional stress. In men, TTS has different, though not yet fully defined, characteristics and clinical course. In fact, men have a higher prevalence of a physical trigger and comorbidities, such as bronchopulmonary or cerebral pathologies, diabetes mellitus, and malignant neoplasms. The hospital course is burdened by a higher rate of cardiogenic shock and mortality. The long-term prognosis is also less favourable in men. Takotsubo syndrome in men characterizes a higher-risk phenotype, which requires close monitoring during hospitalization and careful surveillance during follow-up.

28. Early Menopause, Delayed HRT Tied to Alzheimer's Pathology

Early menopause and delayed initiation of hormone therapy (HT) have been linked to an increase in Alzheimer's disease (AD) pathology in women, a new imaging study shows.

Investigators found elevated levels of tau protein in the brains of women who initiated HT more than 5 years after menopause onset, while those who started the therapy earlier had normal levels.

Tau levels were also higher in women who started menopause before age 45, either naturally or following surgery, but only in those who already had high levels of beta-amyloid.

The findings were published online April 3 in JAMA Neurology.

Hotly Debated

Previous research has suggested the timing of menopause and HT initiation may be associated with AD. However, the current research is the first to suggest tau deposition may explain that link.

"There have been a lot of conflicting findings around whether HT induces risk for Alzheimer's disease dementia or not, and — at least in our hands — our observational evidence suggests that any risk is fairly limited to those rarer cases when women might delay their initiation of HT considerably," senior investigator Rachel Buckley, PhD, assistant investigator in neurology at Massachusetts General Hospital and an assistant professor of neurology at Harvard Medical School, told Medscape Medical News.

The link between HT, dementia, and cognitive decline has been hotly debated since the initial release of findings from the Women's Health Initiative Memory Study, reported 20 years ago.

Since then, dozens of studies have yielded conflicting evidence about HT and AD risk, with some showing a protective effect and others showing the treatment may increase AD risk.

29. Impact of Race and Ethnicity on CVD Risk Factors in Women

Cardiovascular disease is the leading cause of death in women, yet differences exist among certain racial and ethnic groups. Aside from traditional risk factors, behavioral and environmental factors and social determinants of health affect cardiovascular health and risk in women. Language barriers, discrimination, acculturation, and health care access disproportionately affect women of underrepresented races and ethnicities. These factors result in a higher prevalence of cardiovascular disease and significant challenges in the diagnosis and treatment of cardiovascular conditions. Culturally sensitive, peer-led community and health care professional education is a necessary step in the prevention of cardiovascular disease. Equitable access to evidence-based cardiovascular preventive health care should be available for all women

regardless of race and ethnicity; however, these guidelines are not equally incorporated into clinical practice. This scientific statement reviews the current evidence on racial and ethnic differences in cardiovascular risk factors and current cardiovascular preventive therapies for women in the United States.

30. **Sex-Related Differences in Clinical Characteristics and Outcome Prediction Among Patients Undergoing Transcatheter Tricuspid Valve Intervention**

Background

Men and women differ regarding comorbidities, pathophysiology, and the progression of valvular heart diseases.

Objectives

This study sought to assess sex-related differences regarding clinical characteristics and the outcome of patients with severe tricuspid regurgitation (TR) undergoing transcatheter tricuspid valve intervention (TTVI).

Methods

All 702 patients in this multicenter study underwent TTVI for severe TR. The primary outcome was 2-year all-cause mortality.

Results

Among 386 women and 316 men in this study, men were more often diagnosed with coronary artery disease (52.9% in men vs 35.5% in women; $P = 5.6 \times 10^{-6}$). Subsequently, the underlying etiology for TR in men was predominantly secondary ventricular (64.6% in men vs 50.0% in women; $P = 1.4 \times 10^{-4}$), whereas women more often presented with secondary atrial etiology (41.7% in women vs 24.4% in men, $P = 2.0 \times 10^{-6}$). Notably, 2-year survival after TTVI was similar in women and men (69.9% in women vs 63.7% in men; $P = 0.144$).

Multivariate regression analysis identified dyspnea expressed as New York Heart Association functional class, tricuspid annulus plane systolic excursion (TAPSE), and mean pulmonary artery pressure (mPAP) as independent predictors for 2-year mortality. The prognostic significance of TAPSE and mPAP differed between sexes. Consequently, we looked at right ventricular–pulmonary arterial coupling expressed as TAPSE/mPAP and identified sex-specific thresholds to best predict survival; women with a TAPSE/mPAP ratio <0.612 mm/mm Hg displayed a 3.43-fold increased HR for 2-year mortality ($P < 0.001$), whereas men with a TAPSE/mPAP ratio <0.434 mm/mm Hg displayed a 2.05-fold increased HR for 2-year mortality ($P = 0.001$).

Conclusions

Even though men and women differ in the etiology of TR, both sexes show similar survival rates after TTVI. The TAPSE/mPAP ratio can improve prognostication after TTVI, and sex-specific thresholds should be applied to guide future patient selection.