

News in March 2024

1. Women Gain More From Exercise Than Men—and Get Away With Less

When it comes physical activity and exercise, women appear to get a lot more out of it than men, at least when it comes to risk reduction, according to new research published this week.

At equivalent doses of leisure-time physical activity, women have much larger reductions in all-cause and cardiovascular mortality, and they can achieve similar benefits as men with less time spent exercising, report Hongwei Ji, MD (Beijing Tsinghua Changgung Hospital, China), and colleagues this week in the *Journal of the American College of Cardiology*.

“In many ways, I think this lets women off the hook a little bit,” senior investigator Susan Cheng, MD (Smidt Heart Institute/Cedars-Sinai Medical Center, Los Angeles, CA), told TCTMD. “They may carry a lot of burden, and I’m totally generalizing here, in terms of responsibilities at work or responsibilities at home—the traditionally very busy woman in the household who doesn’t feel like she has time to do anything. We’re saying you can get away with less: you can get more out of less. You don’t have to feel like you have to keep up with your male counterparts and exercise 5 hours per week. You can get away with two-and-a-half hours.”

The findings are important as they challenge the “once-size-fits-all” approach currently used to prescribe physical activity to the general population, say investigators.

“It’s a lot for a clinician, never mind a patient, to keep track of what they should be drinking, what they should be eating, and how much exercise they should be getting,” said Cheng. “It’s much easier to have a blanket statement. In many instances, it applies and it’s appropriate. On the other hand, we’re living in a paradoxical age of biomedicine where we recognize that we really do want to personalize medicine down to each individual patient.”

While the days of writing a prescription for exercise and diet specifically tailored to the individual are years away yet, “we have to start with, at least at a basic level, the first order of difference and that is female versus male,” said Cheng.

Carl Lavie, MD (John Ochsner Heart and Vascular Institute, New Orleans, LA), who wasn’t involved in the study, has previously published data showing that women are much less likely than men to engage in leisure-time physical activity, with the largest sex disparities seen in the young and elderly, in Black and Hispanic individuals, and in those with lower incomes.

“Women seem to get substantial benefits at lower levels of exercise, which is a good message, but continue to get even more benefits at higher levels,” he told TCTMD in an email. “So even at levels below the guidelines, women are getting substantial benefits, which hopefully can stimulate them to be more active since generally their physical activity is less.”

He noted that while women tend to get a larger reduction in risk with the same amount of exercise, men tend to be at higher risk for cardiovascular disease, so it’s possible that the absolute benefit could be greater in higher-risk men.

Bigger Benefits Across the Board

The current US and European clinical guidelines recommend 150 to 300 minutes of moderate-intensity physical activity or 75 to 150 minutes of vigorous physical activity each week for health benefits, including a reduction in the risk of coronary heart disease. In the US, the physical activity guidelines from the Office of Disease Prevention and Health Promotion say it’s best to spread that activity out throughout the week and to add in muscle-strengthening activities of all major muscle groups at least 2 days per week.

The guidelines don’t differentiate by sex, though, instead recommending that men and women do the same amount of physical activity. However, as the investigators point out, it’s been well documented that males tend to have greater exercise capacity than females across all age groups, which may be

the result of larger hearts, wider lung airways, and larger muscle fibers, among other differences.

“In physiology labs, we know that males and females perform differently,” she said. “So, it started to make sense when we thought about the study design of this particular paper that we might see something different.”

The study, which uses data from the Centers for Disease Control and Prevention’s National Center for Health Statistics, included 412,413 participants (mean age 43.9 years; 54.7% women). With nearly 5 million person-years of follow-up, there were 39,935 deaths from all causes and 11,670 cardiovascular deaths. Overall, 32.5% of women and 43.1% engaged in regular aerobic exercise, which was defined as meeting or exceeding the 150 weekly minutes of moderate-to-vigorous physical activity (MVPA) each week.

We’re saying you can get away with less, you can get more out of less.

Susan Cheng

In women, regular physical activity compared with inactivity was associated with a 24% lower risk of all-cause mortality, whereas regularly active men had just a 15% reduction compared with inactive men ($P < 0.001$ for interaction by sex). Regular aerobic exercise versus inactivity decreased the risk of cardiovascular mortality by 14% in men compared with 36% in a similar comparison in women ($P < 0.001$ for interaction).

The greatest reduction in all-cause mortality in men was seen at 300 min/week of MVPA, an 18% reduction. With women, a similar reduction in all-cause mortality was seen at just 140 minutes of activity per week, but they made further gains with more exercise. For example, at roughly 300 minutes/week of MVPA, there was a 24% reduction in all-cause mortality risk in women. With vigorous physical activity (VPA), the largest benefit in men was seen at 110 minutes week, a 19% lower risk of all-cause mortality. Women achieved a similar reduction at only 57 minutes per week ($P = 0.004$

for interaction), with a maximum 24% reduction in all-cause mortality in women observed at 110 minutes of VPA each week.

Overall, the survival benefit was consistently higher in women than men when analyzed by exercise frequency, duration per session, and intensity, say researchers.

Additionally, they found that men who regularly hit the gym had an 11% reduction in all-cause mortality compared with those who didn't do strength training. In women, the mortality risk reduction with strength training was 19% compared with women who didn't work out ($P = 0.005$ for interaction).

Personalized Exercise Prescription

To TCTMD, Cheng said the magnitude of difference between men and women surprised the researchers, noting they had expected to see a much smaller gap. She acknowledged the potential for confounding, noting that physical activity is self-reported. Additionally, the confidence intervals are wide, "meaning there's a lot of variation within men and within women," she said.

Still, Cheng suspects it may be time for the physical activity guidelines to consider adopting different recommendations for men and women.

"If anything, I think, when counseling and advising your female as well as male patients, consider that the differences are likely to be quite real," she said. "You can potentially temper some of your advice to your female patients about how hard and how much they really need to do to get a benefit. At the end of the day, anything is better than nothing, and more is better than less."

In an editorial, Wael Jaber, MD, and Erika Hutt, MD (both from Cleveland Clinic, OH), agree that the sex-specific benefit seen in the present study could influence exercise recommendations in major guidelines. It might also encourage more women to engage in physical activity, particularly since the weekly goal is more achievable for those who struggle to find time.

They expand their lens, too, noting that healthcare providers need to push for policies that will reintroduce more casual physical activity into daily routines. In doing so, women would be expected “to reap the most benefits in terms of survival,” Jaber and Hutt write.

2. Metabolic Dysfunction–Associated Fatty Liver Disease and Heart Failure: Sex and Age Differences

BACKGROUND

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a risk factor for heart failure (HF) occurrence, but it remains unclear whether the association between MAFLD and HF differs in different sexes and ages.

METHODS

A total of 96 576 participants of Kailuan Study were included. MAFLD was defined as presence of hepatic steatosis and metabolic dysfunction and classified as mild and significant by ultrasound. Hazard ratios (HRs) were calculated by Cox regression models.

RESULTS

After a median follow-up of 14.0 years, 2939 participants developed HF. Adjusting for confounding factors, mild-MAFLD (HR, 1.27 [95% CI, 1.16-1.39]) and significant-MAFLD (HR, 1.45 [95% CI, 1.31-1.63]) were associated with a higher risk of HF in all participants, and the risk differed by sex ($P_{\text{interaction}} < 0.05$) and age ($P_{\text{interaction}} < 0.001$). Compared with non-MAFLD participants, in women, significant-MAFLD was associated with an 84% (HR, 1.84 [95% CI, 1.43-2.37]) increased risk of HF; however, in men, the risk was 36% (HR, 1.36 [95% CI, 1.20-1.53]). In participants under 45 years, mild-MAFLD and significant-MAFLD had a 55% (HR, 1.55 [95% CI, 1.07-2.25]) and 172% (HR, 2.72 [95% CI, 1.87-3.97]) increased risk of HF; however, in participants over 65 years, even significant-MAFLD did not associate with a higher risk of HF (HR, 1.11 [95% CI, 0.92-1.34]). Afterwards, we stratified all participants by both sex and age and found that the risk of MAFLD-associated

HF decreased with age in men ($P_{\text{interaction}} < 0.05$) and women ($P_{\text{interaction}} < 0.05$), but the sex difference in this risk was only present in participants younger than 45 years ($P_{\text{interaction}} < 0.05$).

CONCLUSIONS

MAFLD greatly increased the risk of HF in women, especially young women. With increasing age, MAFLD-related risk of HF decreased and the difference between men and women disappeared.

3. Cardiac Remodeling After a Hypertensive Pregnancy Following Physician-Optimized BP Self-Management

BACKGROUND

Improved survival following heart transplantation (HT) has led to more recipients contemplating pregnancy, but data on outcomes are limited.

OBJECTIVES

The authors used a national data set to investigate and describe outcomes of pregnancies and deliveries in the United States in HT recipients.

METHODS

Diagnosis and procedure codes from the 2010-2020 Nationwide Readmissions Database identified delivery hospitalizations, history of HT, comorbid conditions, and outcomes. The authors compared rates of severe maternal morbidity (SMM), nontransfusion SMM, cardiovascular SMM (cSMM), and preterm birth from delivery hospitalization between HT recipients and no-HT recipients. The authors evaluated readmission to 330 days postpartum. Logistic and proportional hazard regressions were performed, adjusting for age, socioeconomic and facility characteristics, and clinical comorbidities.

RESULTS

Among 19,399,521 deliveries, 105 were HT recipients. Compared with no-HT, HT recipients were at higher risk for all SMM (24.8% vs 1.7%), nontransfusion SMM (20.8% vs 0.7%), cSMM (7.3% vs 0.12%), and preterm birth (43.3% vs

8.2%), all $P < 0.001$. In adjusted analyses, HT recipients had 16-fold greater odds of SMM, 28-fold greater odds of nontransfusion SMM, 38-fold greater odds of cSMM, and 7-fold greater odds of preterm birth. HT recipients had higher morbidity rates during delivery hospitalization and higher readmission rates within 1 year following delivery (26.9% vs 3.8%; adjusted HR: 6.03 [95% CI: 3.73-9.75]).

CONCLUSIONS

Delivery with history of HT is associated with significantly increased rates of SMM, preterm birth, and hospital readmission. These results provide data regarding pregnancy outcomes for use when counseling patients with HT history who are considering pregnancy or who are pregnant.

4. More Sitting Tied to Greater Death Risk in Older Women

Higher total sitting time and longer mean sitting bout duration are associated with higher all-cause and cardiovascular disease (CVD) mortality risk among older women, according to a study published online Feb. 27 in the *Journal of the American Heart Association*.

Steve Nguyen, Ph.D., from the University of California, San Diego, and colleagues examined the prospective associations of convolutional neural network hip accelerometer posture-classified total sitting time and mean sitting bout duration with all-cause and CVD death in older women. The analysis included 5,856 participants (mean age, 79 years) in the Women's Health Initiative Objective Physical Activity and Cardiovascular Health Study (median, 8.4 years of follow-up).

The researchers found that risks for all-cause death and CVD death were higher for women in the highest total sitting time quartile (>11.6 hours/day) versus the lowest (<9.3 hours/day; adjusted hazard ratios [aHRs], 1.57 and 1.78, respectively). Similar risk was seen when comparing women in the longest mean sitting bout duration quartile (>15 minutes) to the shortest (<9.3 minutes; all-cause death: aHR, 1.43; CVD death: aHR, 1.52). Based on

apparent nonlinear associations for total sitting time, higher all-cause death and CVD death risk occurred after approximately 660 to 700 minutes/day.

"Reducing overall sedentary behavior and interrupting prolonged sitting in addition to promoting physical activity could have large public health benefits in an aging society," the authors write.

5. Diet of Solid Fats, Refined Grains, and Cheese Tied to Hypertensive Disorders of Pregnancy

A dietary pattern of solid fats, refined grains, and cheese is associated with increased odds of any hypertensive disorder of pregnancy and preeclampsia, according to a study published online Feb. 27 in the *Journal of the American Heart Association*.

Luis E. Maldonado, Ph.D., M.P.H., from the Keck School of Medicine at the University of Southern California in Los Angeles, and colleagues conducted a prospective pregnancy cohort study involving 451 predominantly low-income Hispanic/Latina women who completed up to two 24-hour dietary recalls in the third trimester of pregnancy. The associations of two previously derived dietary patterns in this population (solid fats, refined grains, and cheese and vegetables, oils, and fruit) and the Healthy Eating Index 2015 were examined with gestational hypertension, preeclampsia, and any hypertensive disorder of pregnancy.

The researchers found that the solid fats, refined grains, and cheese dietary pattern was associated with increased odds of any hypertensive disorder of pregnancy and preeclampsia when comparing highest to lowest quartiles (odds ratios, 3.99 and 4.10, respectively), while reduced odds of preeclampsia were seen in association with the vegetables, oils, and fruit pattern (odds ratio, 0.32). Inverse associations of vegetables, oils, and fruit and the Healthy Eating Index 2015 with preeclampsia were more pronounced among the overweight prepregnancy body mass index category. Findings for the Healthy Eating Index 2015 were generally nonsignificant.

"Our study contributes novel data and provides direction for dietary counseling for the prevention of hypertensive disorders of pregnancy among a high-risk population," the authors write.

6. Reducing CVD Risk in the Postpartum Period After Adverse Pregnancy Outcomes

Adverse pregnancy outcomes are common among pregnant individuals and are associated with long-term risk of cardiovascular disease. Individuals with adverse pregnancy outcomes also have an increased incidence of cardiovascular disease risk factors after delivery. Despite this, evidence-based approaches to managing these patients after pregnancy to reduce cardiovascular disease risk are lacking. In this scientific statement, we review the current evidence on interpregnancy and postpartum preventive strategies, blood pressure management, and lifestyle interventions for optimizing cardiovascular disease using the American Heart Association Life's Essential 8 framework. Clinical, health system, and community-level interventions can be used to engage postpartum individuals and to reach populations who experience the highest burden of adverse pregnancy outcomes and cardiovascular disease. Future trials are needed to improve screening of subclinical cardiovascular disease in individuals with a history of adverse pregnancy outcomes, before the onset of symptomatic disease. Interventions in the fourth trimester, defined as the 12 weeks after delivery, have great potential to improve cardiovascular health across the life course.

7. Sex-based differences in risk factors for incident myocardial infarction and stroke in the UK Biobank

Aim

This study examined sex-based differences in associations of vascular risk factors with incident cardiovascular events in the UK Biobank.

Methods

Baseline participant demographic, clinical, laboratory, anthropometric, and imaging characteristics were collected. Multivariable Cox regression was used to estimate independent associations of vascular risk factors with incident

myocardial infarction (MI) and ischaemic stroke for men and women. Women-to-men ratios of hazard ratios (RHRs), and related 95% confidence intervals, represent the relative effect-size magnitude by sex.

Results

Among the 363 313 participants (53.5% women), 8470 experienced MI (29.9% women) and 7705 experienced stroke (40.1% women) over 12.66 [11.93, 13.38] years of prospective follow-up. Men had greater risk factor burden and higher arterial stiffness index at baseline. Women had greater age-related decline in aortic distensibility. Older age [RHR: 1.02 (1.01–1.03)], greater deprivation [RHR: 1.02 (1.00–1.03)], hypertension [RHR: 1.14 (1.02–1.27)], and current smoking [RHR: 1.45 (1.27–1.66)] were associated with a greater excess risk of MI in women than men. Low-density lipoprotein cholesterol was associated with excess MI risk in men [RHR: 0.90 (0.84–0.95)] and apolipoprotein A (ApoA) was less protective for MI in women [RHR: 1.65 (1.01–2.71)]. Older age was associated with excess risk of stroke [RHR: 1.01 (1.00–1.02)] and ApoA was less protective for stroke in women [RHR: 2.55 (1.58–4.14)].

Conclusion

Older age, hypertension, and smoking appeared stronger drivers of cardiovascular disease in women, whereas lipid metrics appeared stronger risk determinants for men. These findings highlight the importance of sex-specific preventive strategies and suggest priority targets for intervention in men and women.

8. Risk Factor Control Worse in Women Than Men in ISCHEMIA Trial

ISCHEMIA trial, women with chronic coronary disease received less-intense guideline-directed medical therapy (GDMT) overall compared with men and were thus less likely to achieve various goals for risk factor control, researchers report.

Women also had lower rates of revascularization that could be explained by lower rates of obstructive CAD on angiography, but clinical outcomes were no

different between sexes, according to researchers led by Harmony Reynolds, MD (NYU Langone Health, New York, NY).

TCTMD's Quick Takes: Dr. Harmony Reynolds

It was surprising that female patients were treated less aggressively with medical therapy in the context of the trial, which had algorithms for each treatment target in the protocol and included some monitoring of site performance during the study, Reynolds told TCTMD. “I would not have expected to see goal attainment be so different.”

She noted, however, that the undertreatment of women with coronary disease is a “known phenomenon” that has been seen in prior studies, including other clinical trials. And it doesn’t appear to be related to poorer medication adherence in women. Although women had slightly worse adherence in the ISCHEMIA trial, the difference compared with men was not that great, she said.

“I have to assume that there’s some kind of implicit bias. I can’t rule out, of course, that the women want less-intensive therapy, but I have a feeling that this relates to implicit bias among physicians [who think] that women are at lower risk,” Reynolds said. “As we show in this paper, women are not at lower risk. Maybe they should be if they’re treated as aggressively as men, but they aren’t at lower risk.”

The findings, published online this week in the *Journal of the American Heart Association*, provide “one more reminder that we need to force ourselves to be attentive to medical therapy goals at every visit for every patient,” Reynolds said. “We need to be more attentive to making sure that all our patients are getting the same aggressive medical therapy for coronary artery disease. We know medical therapy works, and we need to apply it rigorously.”

Sex Differences in Chronic Coronary Disease

Women with chronic coronary disease are generally older with more comorbidities and less obstructive CAD than their male counterparts. Prior studies have shown that their risk of adverse cardiovascular outcomes is similar, however.

Previous research also has demonstrated that women with chronic coronary disease are less likely to undergo revascularization than are men, and may have poorer outcomes when they do get revascularized. It's unclear how much of this treatment disparity can be traced to differences in ischemia severity between sexes and, in the clinical trial setting, whether protocolized care may impact the gaps in use of revascularization or GDMT.

To explore these issues, Reynolds et al delved into the ISCHEMIA trial, which included 5,179 patients (median age 64 years; 22.6% women) with chronic coronary disease, preserved ejection fraction, and moderate-to-severe ischemia on stress testing randomized to an initial invasive strategy or conservative management. The main results showed that the risk of adverse cardiovascular outcomes didn't differ between strategies.

We need to be more attentive to making sure that all our patients are getting the same aggressive medical therapy for coronary artery disease.Harmony Reynolds

The current analysis highlights some key differences between men and women in the trial. In the invasive arm, women and men were equally like to undergo catheterization, although women had a lower rate of revascularization at any point during follow-up (73.4% vs 81.2%; $P < 0.001$). That can be tied to a lower severity of coronary disease among women, who were more likely to have no stenosis $\geq 50\%$ on angiography (12.3% vs 4.5%) and less likely to multivessel (60.0% vs 74.8%) or three-vessel disease (29.8% vs 42.7%; $P < 0.001$ for all) compared with men.

Catheterization rates also were similar by sex in the conservative arm of the trial. Revascularization rates didn't differ between women and men overall in

this group, but among the subset who underwent catheterization, revascularization was less frequent in women (72.3% vs 82.3%; $P = 0.007$).

As seen in prior studies, use of GDMT overall was lower in women than in men, with fewer risk factor goals achieved by the end of the trial. For instance, women were significantly less likely to attain a systolic blood pressure goal < 140 mm Hg (73.6% vs 77.9%) or an LDL cholesterol goal < 70 mg/dL (50.2% vs 61.3%), and to be treated with aspirin or an aspirin alternative (95.6% vs 97.2%), “despite protocolized trial guidance on medical therapy,” Reynolds et al report. Of note, women were less likely than men to be treated with a high-intensity statin (60.7% vs 64.3%; $P = 0.025$), and had a lower rate of achieving an HbA1c level below 8%, although this was not a specified goal of therapy in the trial.

Women scored lower on a scale of medication adherence than did men, but the difference was not that great, Reynolds said.

“Although we do not have access to detailed information about dose titration in response to blood pressure and laboratory values in the ISCHEMIA trial, analysis of the relationship between risk factor goal attainment and outcomes in the trial is ongoing,” the investigators write. “Nevertheless, the imperative to achieve equitable use of GDMT implementation among women with chronic coronary disease is both an important challenge and an opportunity for improved clinical outcomes.”

Room for Improvement

Despite the suboptimal use of GDMT in women observed in the trial, the rate of the primary endpoint (CV death, MI, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest) was no different between the sexes—14.8% in women and 14.3% in men (adjusted HR 0.93; 95% CI 0.77-1.13). There were similar results for other outcomes, with the exception of periprocedural MI, which was less frequent in women (1.0% vs 2.2%; adjusted HR 0.40; 95% CI 0.21-0.76), consistent with lower rates of revascularization.

“It seems like there’s not much going on there, but I think that under the surface, there’s quite a lot going on there because women have less extensive coronary disease, and that is a powerful predictor of outcomes in stable coronary disease and within the ISCHEMIA trial,” Reynolds said. Counterbalancing that lower risk and resulting in comparable outcomes, however, is that women are also older on average, with a higher burden and poorer control of risk factors.

There shouldn’t really be these discrepancies.Eugenia Gianos

Eugenia Gianos, MD (Northwell Health, New York, NY), chair-elect of the American College of Cardiology’s Prevention of Cardiovascular Disease Council, agreed with that assessment, adding that the differences in the intensity of GDMT between the sexes were surprising and disappointing in the context of ISCHEMIA, even if such disparities have been observed in prior studies.

She, too, mentioned the possible impact of bias on the part of treating physicians to explain the findings, but also said it could be that there are differences stemming from patients declining or discontinuing their medications.

Overall, though, “there’s a lot to be figured out still as to why those differences were there,” Gianos said, noting that there was a low proportion of women in the trial and a lack of information on specific drugs or doses used for GDMT.

Nonetheless, “the reality is that nowadays we have all of the therapies needed to get people to goal, so there shouldn’t really be these discrepancies, and maybe we just need more education of providers about potential biases or [about] the barriers faced by patients in terms of adherence and uptake,” Gianos said, calling for additional high-level research focused on sex disparities.

To underscore the importance of medical therapy in chronic coronary disease, Reynolds alluded to the treatment of heart failure with reduced ejection

fraction, a field that “is moving towards being more aggressive early and increasing multiple drugs at the same visit with the idea that you will achieve better outcomes if you get to goals faster. Perhaps here it’s the same story—that we need to focus on getting our therapeutic armamentarium implemented and implemented at a level that’s going to be useful right away instead of introducing things step by step.”

9. Statin Therapy in Heart Failure With Preserved Ejection Fraction: The Need for Randomized Evidence*

Randomized evidence investigating the role of statin therapy in chronic heart failure has been restricted to heart failure with reduced ejection fraction (HFrEF). The 2 major randomized clinical trials, namely CORONA (Rosuvastatin in Older Patients with Systolic Heart Failure)¹ and GISSI HF (Effect of rosuvastatin in patients with chronic heart failure),² conducted in patients with HFrEF with and without ischemic heart disease failed to demonstrate efficacy of statin therapy in reducing both atherothrombotic and heart failure related events. While trials in HFrEF have been largely neutral, the role of statins in heart failure with preserved ejection fraction (HFpEF) has not been systematically investigated. Most previous studies evaluating the relationship between statin use and outcomes in HFpEF have been observational in nature and are limited either by small sample size, inability to reliably differentiate the 2 main heart failure phenotypes (ie, HFrEF and HFpEF) and methodological limitations such as confounding by indication.³

It is in this context that the study performed by Orkaby et al⁴ gains importance as the investigators have performed comparative effectiveness research evaluating the role of statins in HFpEF using nationwide data from the Veterans Health Administration. After excluding patients with prevalent atherosclerotic cardiovascular disease (ASCVD) and baseline statin use, the authors identified 7,970 veterans with HFpEF, of which 47% were started on statin during the follow-up period. Over a median follow-up of 6 years, statin use was associated with a 22% relative risk reduction in all-cause mortality. Additionally, statin use was associated with a lower hazard for major adverse

cardiovascular events (MACE) (HR: 0.79; 95% CI: 0.74-0.84), all-cause hospitalizations (HR: 0.69; 95% CI: 0.60-0.80), and heart failure related hospitalizations (HR: 0.72; 95% CI: 0.59-0.88).

This hypothesis-generating study overcomes several limitations of prior observational studies. Firstly, the nationwide Veteran Affairs electronic health care records provide a unique opportunity to reliably study HFpEF at the population level due to the availability of serial left ventricular ejection fraction measurements and a validated algorithm with high specificity for identification of HFpEF.⁵ Most population-based studies have merely used ICD codes for HFpEF case ascertainment which lacks specificity. Secondly, the investigators had employed the 'new-user design' to help align patients at a unified time to begin follow-up and to maintain the temporality between exposure and covariates.⁶ Furthermore, in order to minimize information bias, the authors merged Veteran Affairs data with Medicare and Medicaid data. The authors had also rightly chosen a prolonged follow-up period to allow for long-term effects of statin exposure on outcomes. Finally, the 2 comparison groups of statin and non-statin users had significant differences in baseline characteristics. The investigators appropriately used the overlap propensity score weighting method to achieve a good balance on the mean of important covariates between 2 groups without modifying the target population. This is critical for reducing indication bias and increasing the precision of results; however, statistical inference should take into account the fact that balance on the mean may not result in a complete adjustment for confounding.⁷

While the study answers important questions related to statin exposure on outcomes in HFpEF, it also generates important observations on the plausible mechanisms of statin efficacy. Despite the exclusion of patients with prevalent ASCVD, the event rates for MACE during the median follow-up of 6 years were 60.1% for the entire cohort. This is strikingly high and translates to an annual event rate of c.10% in contrast to 2% per year in primary prevention trials.⁸ Greater than 75% of the studied cohort were either current or former smokers (<20% in statin trials for primary prevention) and only 25% of the

patients had a ASCVD risk score of <5%, signifying that this is plausibly a population at very high risk for MACE than the general population or those recruited in primary prevention trials. This could also explain the reason for the clinical benefits and the magnitude of treatment effects realized with statin exposure in this patient population. These findings coupled with interaction effect of statin with ASCVD risk category, with point estimates favoring lower hazard for MACE in the group with high ASCVD risk category suggest an effect mediated by reduction in atherothrombotic events as opposed to statin pleiotropy.

Some of the limitations of the study include the issues faced by all observational studies despite the robust study design. Individuals initiated on statin will differ in several ways from those who did not get one. Individuals in the nonuser group might have contraindications, including frailty and while overlap weighting methods adjust for the known differences between the 2 groups, there may still be residual confounding from unmeasured variables.

This well-conducted study has yielded important hypothesis-generating observations on the clinical efficacy of statin for primary prevention in a well-defined real-world HFpEF cohort with reliable long-term follow-up. We agree with the authors on the need for randomized evidence to confirm these important findings. However, such a randomized controlled trial would be extremely challenging to conduct as it would necessitate recruitment of patients with no indication for statin, that is, nonischemic HFpEF with low risk for ASCVD (69% of the participants in EMPEROR-PRESERVED (Empagliflozin in Heart Failure with a Preserved Ejection Fraction) trial were already on statin therapy prior to randomization).⁹ Such a trial would also reliably answer the question of statin pleiotropy in HFpEF. Finally, the study findings also emphasize the importance of aggressive primary prevention in patients with HFpEF with intermediate and high risk for ASCVD in clinical practice, where the uptake of statins is still far from optimal!

10. Hypertensive Disorders of Pregnancy: Innovative Management Strategies

Hypertensive disorders of pregnancy (HDP) complicate 13% to 15% of pregnancies in the United States. Historically marginalized communities are at increased risk, with preeclampsia and eclampsia being the leading cause of death in this population. Pregnant individuals with HDP require more frequent and intensive monitoring throughout the antepartum period outside of routine standard of care prenatal visits. Additionally, acute rises in blood pressure often occur 3 to 6 days postpartum and are challenging to identify and treat, as most postpartum individuals are usually scheduled for their first visit 6 weeks after delivery. Thus, a multifaceted approach is necessary to improve recognition and treatment of HDP throughout the peripartum course. There are limited studies investigating interventions for the management of HDP, especially within the United States, where maternal mortality is rising, and in higher-risk groups. We review the state of current management of HDP and innovative strategies such as blood pressure self-monitoring, telemedicine, and community health worker intervention.

Highlights

- HDP complicate 13 to 15% of all pregnancies in the United States.
- Individuals with HDP require more frequent and intensive peripartum management than routine standard of care.
- Innovative management strategies are needed, but the best approach, timing, frequency, and intensity are uncertain.
- Blood pressure self-monitoring, telemedicine, and community health worker intervention may be novel approaches to HDP

11. Sex Differences in Physical Activity and CV Mortality Risk

Study Questions:

Do health benefits derived from physical activity differ by sex?

Methods:

Data were collected by the Centers for Disease Control and Prevention and the National Center for Health Statistics from all 50 states and the District of Columbia. Pooled data from records of 646,279 adult participants of the National Health Interview Survey for years 1997–2017 were linked to the National Death Index records through December 31, 2019. Participants with pre-existing diagnoses of coronary heart disease, myocardial infarction, stroke, emphysema, chronic bronchitis, or cancer; limitations in activities of daily living; missing data on physical activity; or missing data on follow-up status or key covariates were excluded. Participants with outcomes occurring within the first 2 years of follow-up were also excluded. The remaining 412,413 participants (55% female, ages 44 ± 17 years) comprised the study sample. Leisure-time physical activity was collected via surveys. Physical activity was examined by frequency, duration, intensity, and type. The primary outcomes were all-cause and cardiovascular (CV) mortality, from 1997–2019.

Results:

Of the 412,413 participants in this study, 54.7% were female, 14.4% identified as Black, and 18.4% identified as Hispanic. The baseline mean age was 43.9 ± 16.6 years. Over a total 4,911,178 person-years of follow-up, 39,935 all-cause deaths occurred (8.1 per 1,000 person-years) including 11,670 CV deaths (2.4 per 1,000 person-years). Regular leisure-time physical activity compared to inactivity was associated with a 24% (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.73-0.80) and 15% (HR, 0.85; 95% CI, 0.82-0.89) lower risk of all-cause mortality in females and males, respectively (Wald $F = 12.0$, sex interaction $p < 0.001$). Males reached their maximal survival benefit of HR 0.81 from 300 min/wk of moderate-to-vigorous physical activity, while females achieved similar benefit at 140 min/wk and then continued to reach a maximum survival benefit of HR 0.76 also at approximately 300 min/wk. Sex-specific findings were similar for CV death (Wald $F = 20.1$, sex interaction $p < 0.001$) and consistent across all measures of aerobic activity

as well as muscle strengthening activity (Wald $F = 6.7$, sex interaction $p = 0.009$).

Conclusions:

The authors conclude that females compared to males derived greater gains in all-cause and CV mortality risk reduction from equivalent doses of leisure-time physical activity. These findings could enhance efforts to close the “gender gap” by motivating especially females to engage in any regular leisure-time physical activity.

Perspective:

These data support the significant benefits from physical activity among women and men, suggesting that clinical providers counsel both men and women to obtain regular activity. In addition, public health interventions are needed to assist equity in access to venues for physical activity.

12. Anemia and Sex Disparity in Operative Mortality After CABG

Study Questions:

Women undergoing coronary artery bypass grafting (CABG) have higher operative mortality than men. What is the relationship between intraoperative anemia (nadir intraoperative hematocrit), CABG operative mortality, and sex?

Methods:

A cohort study of 1,434,225 isolated primary CABG patients (344,357 women) from the Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS-ACSD) (2011–2022) was used for analysis. Patients were included if they underwent primary isolated CABG during the study period. Patients were excluded if they required resuscitation prior to surgery, if they underwent emergent or salvage surgery, or if they underwent re-operative CABG. Baseline demographics were stratified both by sex and intraoperative anemia,

with hematocrit values stratified based on the World Health Organization anemia classification as follows: none to mild (nadir intraoperative hematocrit $\geq 33.0\%$), moderate (intraoperative hematocrit $24.0\% < 19.5\%$), to severe (nadir intraoperative hematocrit $19.5\% < 19.5\%$).

The primary outcome was operative mortality. The attributable risk (AR) (the risk-adjusted strength of the association of female sex with CABG outcomes) for the primary outcome was calculated. Causal mediation analysis derived the total effect of female sex on operative mortality risk and the proportion of that effect mediated by intraoperative anemia.

Results:

Women had lower median nadir intraoperative hematocrit (22.0%, interquartile range [IQR] 20.0-25.0% vs. 27.0% [IQR 24.0-30.0], standardized mean difference 97.0%) than men. Women had higher operative mortality than men (2.8% vs. 1.7%, $p < 0.001$). The AR of women for operative mortality was 1.21 (95% confidence interval [CI], 1.17-1.24). After adjusting for nadir intraoperative hematocrit, AR was reduced by 43% (1.12; 95% CI, 1.09-1.16). Intraoperative anemia mediated 38.5% of the increased mortality risk associated with female sex (95% CI, 32.3-44.7%). Spline regression showed a stronger association between operative mortality and nadir intraoperative hematocrit at hematocrits below 22.0% ($p < 0.001$).

Conclusions:

In this analysis of 1,434,225 patients (344,357 women) from the STS-ACSD, the investigators found that women had a higher risk of operative mortality after CABG compared with men, and that the association of gender with mortality was mediated to a large extent by intraoperative anemia with worse outcomes in women. The association between operative mortality in women and anemia was strongest at intraoperative nadir hematocrit below 22.0%. Those results were solid in all the sensitivity analyses.

Perspective:

Prior studies have shown more severe intraoperative anemia, and higher operative mortality in CABG patients with small body size, a category in which women are disproportionately represented. Preoperative hematocrit is strongly correlated with nadir intraoperative hematocrit and is significantly lower in women compared to men even when accounting for the body size differences between sexes and is associated with elevated major adverse cardiac events in women with ischemic heart disease. Due to the combination of lower starting hematocrit and smaller body size, women are more susceptible to severe intraoperative anemia than men. These results indicate that the sex and gender difference in severe intraoperative anemia largely explains the increased CABG operative mortality in women. As such, avoiding severe intraoperative anemia and hematocrit below 22.0% may help close the gap between men and women in CABG outcomes.

13. Physician-Optimized Postpartum Hypertension Treatment - POP HT

Contribution To Literature:

The POP-HT trial showed that in women with hypertensive pregnancy, a telehealth initiative to rapidly optimize postpartum anti-HTN medications was associated with long-term, potentially beneficial changes in cardiac structure compared with usual care.

Description:

The goal of this secondary analysis was to determine the effect on cardiac remodeling of intensive, telehealth-based management of hypertension (HTN) versus usual postpartum care following hypertensive pregnancy.

Study Design

- Randomized

- Single-center
- Open-label
- Secondary analysis

Pregnant women with gestational HTN or pre-eclampsia were randomized in 1:1 fashion to anti-HTN medication adjustment by a remote team of cardiologists and obstetricians guided by minimum-daily home blood pressure (BP) readings (n = 109) or usual postpartum care comprising a family physician and/or midwife (n = 107). A transthoracic echocardiogram (TTE) was performed at baseline (days 1 to 6 postpartum) and final study visit (6 to 9 months postpartum). Cardiac magnetic resonance imaging (CMR) was performed at the final visit only.

- Total number of enrollees: 216 with baseline TTE
- Duration of follow-up: 9 months postpartum
- Mean patient age: 33 years

Inclusion criteria:

- Age ≥ 18 years
- Gestational HTN (i.e., new onset at ≥ 20 weeks of gestation) or pre-eclampsia
- Anti-HTN medication requirement at discharge

Exclusion criteria:

- Significant kidney or liver disease that, in the investigator's judgment, may limit medication adjustment
- Chronic hypertension preceding pregnancy or 20 weeks of gestation
- Other comorbid conditions that may affect patient safety, ability to participate, or influence results during the trial period

Other salient features/characteristics:

- Mean antenatal BP: 118/72 mm Hg
- Pre-eclampsia: 60%

- Primiparous: 66%
- Emergency cesarean section: 40%
- Repeat TTE obtained, intervention vs. usual care: 93% vs. 80%
- CMR obtained, intervention vs. usual care: 85% vs. 76%

Principal Findings:

Mean difference in baseline-adjusted TTE measures at 9 months, intervention vs. usual care:

- Left ventricular ejection fraction (LVEF): 65.57% vs. 63.72%, +1.79 (95% confidence interval [CI] 0.84 to 2.75), $p < 0.001$
- Relative wall thickness: 0.27 vs. 0.33, -0.06 (95% CI -0.07 to -0.05), $p < 0.001$
- LV end-diastolic volume index (LVEDVi): 59.03 mL/m² vs. 63.68 mL/m², -4.74 (95% CI -6.23 to -3.26), $p < 0.001$
- Average E/E': 6.05 vs. 6.61, -0.52 (95% CI -0.97 to -0.06), $p = 0.024$
- Left atrial volume index: 21.74 mL/m² vs. 25.98 mL/m², -4.36 (95% CI -5.52 to -3.21), $p < 0.001$

Mean difference in CMR measures at 9 months, intervention vs. usual care:

- LVEF: 64.37% vs. 61.85%, +2.61 (95% CI 1.31 to 3.92), $p < 0.001$
- Right ventricular EF: 60.93% vs. 58.32%, +2.76 (95% CI 1.44 to 4.09), $p < 0.001$
- LVEDVi: 66.27 mL/m² vs. 70.07 mL/m², -3.87 (95% CI -6.77 to -0.98), $p = 0.009$
- LV mass index: 39.18 mL/m² vs. 45.48 mL/m², -6.37 (95% CI -7.99 to -4.74), $p < 0.001$

Interpretation:

The POP-HT trial showed that a telehealth intervention of intensive anti-HTN medication titration was more effective than usual care in lowering 9-month ambulatory BP. Although exploratory and not adjusted for multiplicity, this

secondary analysis demonstrates more favorable echocardiographic and CMR measures of cardiac remodeling, diastology, and biventricular systolic function in the intervention arm. Hypertensive disorders of pregnancy are associated with exaggerated and persistent LV remodeling, which in normotensive gestation typically resolves rapidly postpartum. The consequent LV hypertrophy and diastolic dysfunction is associated with subsequently developing chronic HTN and may increase long-term risk for adverse cardiovascular events. Although the absolute mean difference of each measure was small, the overall cohort was young, and these differences may compound over decades toward very different cardiac phenotypes.

Notably, only 12% of patients in this study remained on anti-HTN medication at their 6- to 9-month visit, and median treatment duration in the intervention arm was only 39 days. These results therefore suggest that early postpartum BP optimization may induce rapid cardiac remodeling associated with more favorable long-term cardiovascular risk.

14. Rheumatoid Arthritis and Cardiovascular Complications During Delivery

BACKGROUND AND AIMS

Persons with rheumatoid arthritis (RA) have an increased risk of obstetric-associated complications, as well as long-term cardiovascular (CV) risk. Hence, the aim was to evaluate the association of RA with acute CV complications during delivery admissions.

METHODS

Data from the National Inpatient Sample (2004-2019) were queried utilizing ICD-9 or ICD-10 codes to identify delivery hospitalizations and a diagnosis of RA.

RESULTS

A total of 12 789 722 delivery hospitalizations were identified, of which 0.1% were among persons with RA (n = 11 979). Individuals with RA, vs. those

without, were older (median 31 vs. 28 years, $P < .01$) and had a higher prevalence of chronic hypertension, chronic diabetes, gestational diabetes mellitus, obesity, and dyslipidaemia ($P < .01$). After adjustment for age, race/ethnicity, comorbidities, insurance, and income, RA remained an independent risk factor for peripartum CV complications including preeclampsia [adjusted odds ratio (aOR) 1.37 (95% confidence interval 1.27-1.47)], peripartum cardiomyopathy [aOR 2.10 (1.11-3.99)], and arrhythmias [aOR 2.00 (1.68-2.38)] compared with no RA. Likewise, the risk of acute kidney injury and venous thromboembolism was higher with RA. An overall increasing trend of obesity, gestational diabetes mellitus, and acute CV complications was also observed among individuals with RA from 2004-2019. For resource utilization, length of stay and cost of hospitalization were higher for deliveries among persons with RA.

CONCLUSIONS

Pregnant persons with RA had higher risk of preeclampsia, peripartum cardiomyopathy, arrhythmias, acute kidney injury, and venous thromboembolism during delivery hospitalizations. Furthermore, cardiometabolic risk factors among pregnant individuals with RA rose over this 15-year period.

15. **Sex and Age Characteristics in Acute or Chronic Myocarditis: A Descriptive, Multicenter Cohort Study**

Background

Understanding the clinical features of myocarditis in various age groups is required to identify age-specific disease patterns.

Objectives

The objective of this study was to examine differences in sex distribution and clinical outcomes in patients with myocarditis of various ages.

Methods

Patients with acute or chronic myocarditis in 3 centers in Berlin, Germany from 2005 to 2021 and in the United States (National Inpatient Sample) from 2010 to 2019 were included. Age groups examined included “prepubescent” (below 11 years for females and below 13 years for males), adolescents (11 [female] or 13 [male] to 18 years), young adults (18-35 years), “middle-aged adults” (35-54 years), and older adults (age >54 years). In patients admitted to the hospital, hospital mortality, length of stay, and medical complication rates were examined.

Results

Overall, 6,023 cases in Berlin and 9,079 cases in the U.S. cohort were included. In both cohorts, there were differences in sex distribution among the 5 age categories, and differences in the distribution were most notable in adolescents (69.3% males vs 30.7% females) and in young adults (73.8% males vs 26.3% females). Prepubescent and older adults had the highest rates of in-hospital mortality, hospital length of stay, and medical complications. In the Berlin cohort, prepubescent patients had higher levels of leukocytes ($P < 0.001$), antistreptolysin antibody ($P < 0.001$), and NT-proBNP ($P < 0.001$) when compared to young adults.

Conclusions

In this study, we found that sex differences in myocarditis and clinical features of myocarditis were age-dependent.

Introduction

One consistent characteristic of clinical myocarditis is the report of sex differences with more males having myocarditis than females.¹⁻⁶ Studying the clinical nature of myocarditis by sex and age is necessary to learn about risk factors and patterns of disease. In addition to having a higher incidence of myocarditis, men also tend to have a more severe clinical course compared to

women.^{7,8} Various potential contributing factors have been reported for this sex difference including the influence of sex hormones.⁹ It has been shown that the immune response, in particular innate immune signaling molecules on mast cells, macrophages, and T cells, differs in the inflamed myocardium by sex.^{4,10-12} Also, men with myocarditis tend to develop more myocardial fibrosis on cardiac magnetic resonance (CMR) imaging, which has been suggested to be a potential explanation for their higher risk of arrhythmias and sudden cardiac death.⁸ Fibrotic remodeling in patients with myocarditis has been demonstrated in animal models to be testosterone-dependent.^{13,14} Other factors that may affect the clinical course in myocarditis are sex-specific differences in gene expression, as observed in patients with heart failure.^{1,15-18}

Since the beginning of the COVID-19 pandemic, myocarditis has gained significant public attention due to its increasing incidence caused by SARS-CoV2 infection and, to a much lesser degree, mRNA vaccines.¹⁹ Notably, there has been a significantly higher occurrence of myocarditis in young men compared to women among both COVID-19 and vaccine-related cases. The underlying reasons for this phenomenon remain unknown.

Overall, data is limited on the differences in clinical characteristics of myocarditis in various age groups. There have been 3 inpatient registry studies of more than 2,500 patients hospitalized for myocarditis, reporting on hospital length of stay (LOS), medical complications, and mortality outcomes.²⁰⁻²² However, these studies published either preliminary data or were focused on patients below the age of 20. Furthermore, laboratory and echocardiographic markers were not included.

To evaluate sex differences and clinical features in patients with myocarditis according to age, we performed a multicenter analysis of clinical data from over 15,000 patients diagnosed with myocarditis across all age groups presenting to either 3 large tertiary care centers in Berlin, Germany from 2005 to 2021 ("Berlin cohort") or hospitals in the United States from 2010 to 2019 ("U.S. cohort").

Methods

Study population

The study population included patients diagnosed with myocarditis who were treated at 3 multidisciplinary tertiary care hospitals in Berlin, Germany, as well as a sample of data from U.S. hospitals. The study was approved by the local ethics committees. The diagnosis of myocarditis in the Berlin cohort was made based on the recommendations of the European Society of Cardiology.²³ Acute vs chronic myocarditis was based on the duration of clinical symptoms with symptoms persisting longer than 3 months being classified as chronic.²³ In the Berlin cohort, clinicians diagnosed myocarditis by a combination of clinical, laboratory, electrocardiographic findings, endomyocardial biopsies (EMB, 25.0% of the Berlin cohort), and/or CMR (16.0% of the Berlin cohort). Patients with a past medical history of myocarditis or missing baseline data were excluded from the study (**Figure 1**). The Berlin cohort was further divided into a subgroup of patients with myocarditis who received an EMB (“biopsy-proven myocarditis”).

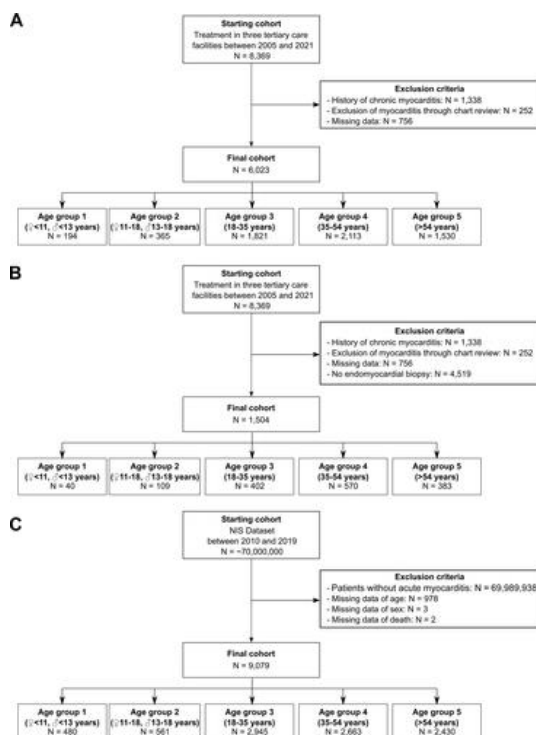


Figure 1

Study Subject Flow Diagram

(A) Berlin cohort, (B) Berlin cohort, biopsy proven, (C) U.S. cohort.

Age groups

The study cohort was divided into 5 age groups based on common age definitions in the medical literature: Age group 1 (“prepubescent”) was defined based on prepubescent age, which is defined as below 11 years for female and below 13 years for male patients.²⁴⁻²⁶ Age group 2 (“adolescents”) ranged from 11 (female) or 13 (male) to 18 years; age group 3 (“young adults”) between 18 and 35 years; age group 4 (“middle-aged adults”) between 35 and 54 years; and age group 5 (“older adults”) was defined as age above 54 years based on the average age of menopause in women.²⁷ Age group 3 was the reference age group used for comparison purposes.

Primary and secondary outcomes

Within each age group, the sex distribution in patients with myocarditis was examined (primary outcome). After the exclusion of outpatient cases, hospital mortality, hospital LOS, and medical complication rates (secondary outcomes) were examined in patients admitted to the hospital for inpatient treatment. Hospital mortality was defined as a mortality event that occurred during the patient's hospital stay. Hospital LOS was defined as the number of days between hospital admission and discharge. Medical complications were defined as the occurrence of malignant arrhythmias, cardiogenic shock, heart transplantation, or the implantation of a left ventricular assist device, extracorporeal membrane oxygenation, Impella micro-axial pump, or intra-aortic balloon pump.

Exploratory analysis in the Berlin cohort

With an exploratory intent, the level of laboratory values, such as C-reactive protein (CRP), troponin T, leukocytes, antistreptolysin antibody, and NT-pro

BNP were analyzed by age group. Additionally, left ventricular ejection fraction (LVEF) within a subgroup of patients who had documented transthoracic echocardiograms (N = 1,171) was analyzed by age. Causes of death were manually retrieved from the medical record for deceased patients, and in all patients who received an EMB and died, the pathologic EMB reports were retrieved.

Statistical analysis

Normality was assessed using Shapiro-Wilk analysis. Categorical and continuous variables were compared using chi-square tests and Student's *t*-tests (normally distributed) or Fisher's exact test and Wilcoxon-Mann-Whitney U-test (non-normally distributed), respectively. Normally distributed continuous variables are expressed as mean \pm SD, non-normally distributed variables as median (IQR), and categorical variables as frequency (percentage). Results are presented as adjusted odds ratios (ORs) or incidence rate ratios (IRR) with 95% CIs and *P* values. A 2-tailed *P* value <0.05 was considered statistically significant. A Poisson regression model was used to analyze hospital LOS between age groups, Cox proportional hazard model to analyze hospital mortality, and logistic regression to analyze medical complication rates. Data analyses were performed using R Core Team 2020.

Results

In the Berlin cohort, a total of 6,023 patients were treated between January 2005 and March 2021 with a primary diagnosis of acute or chronic myocarditis, while there were 9,079 patients in the U.S. cohort between 2010 and 2019. The following age distributions were observed in the Berlin and the U.S. cohort: 194 patients (3.2%) and 480 (5.3%) were in age group 1, 365 (6.1%) and 561 (6.2%) in age group 2, 1,821 (30.2%) and 2,945 (32.4%) in age group 3, 2,113 (35.1%) and 2,663 (29.3%) in age group 4, and 1,530 (25.4%) and 2,430 (26.8%) in age group 5 (**Figure 1**). Within the Berlin cohort, 3,944 patients had acute myocarditis and 2,079 patients had chronic myocarditis. Within both cohorts, the average Charlson comorbidity index of the study

cohort was 1 (0-2). One thousand eight hundred sixty-four (12.3%) received an EMB, while a CMR was performed in 1,056 (7%) patients (**Table 1**). In the Berlin cohort, the rate of performed EMBs gradually decreased from 89 (38.2%) in 2005 to 38 (31.9%) in 2021, while the rate of CMR has more than doubled from 25 (10.7%) to 28 (23.5%) within the same time period (**Supplemental Table 2**).

Table 1 Baseline Characteristics and Cardiac Procedures Stratified by Age Groups in the Berlin and U.S. Cohorts

	Age Group 1 (n = 674)	Age Group 2 (n = 926)	Age Group 3 (n = 4,766)	Age Group 4 (n = 4,776)	Age Group 5 (n = 3,960)	Overall (n = 15,102)
Baseline characteristics						
CCI	1 (0, 1)	0 (0, 1)	0 (0, 1)	1 (0, 2)	1 (0, 3)	1 (0, 2)
CCI ≤3	662 (98.2%)	910 (98.3%)	4,637 (97.3%)	4,445 (93.1%)	3,220 (81.3%)	13,874 (91.9%)
CCI >3	12 (1.8%)	16 (1.7%)	129 (2.7%)	331 (6.9%)	740 (18.7%)	1,228 (8.1%)
Cardiac procedures						
Endomyocardial biopsy	70 (10.4%)	149 (16.1%)	498 (10.4%)	681 (14.3%)	466 (11.8%)	1,864 (12.3%)
Cardiac catheterization	1 (0.1%)	6 (0.6%)	7 (0.1%)	31 (0.6%)	41 (1%)	86 (0.6%)

Table 1 Baseline Characteristics and Cardiac Procedures Stratified by Age Groups in the Berlin and U.S. Cohorts

	Age Group 1 (n = 674)	Age Group 2 (n = 926)	Age Group 3 (n = 4,766)	Age Group 4 (n = 4,776)	Age Group 5 (n = 3,960)	Overall (n = 15,102)
Cardiac	43 (6.4%)	153 (16.5%)	382 (8%)	302 (6.3%)	176 (4.4%)	1,056
MRI						(7%)

Values are median (IQR) or n (%).

Age group 1: ♀ <11 or ♂ <13 years of age; age group 2: ♀ 11 to 18 or ♂ 13 to 18 years of age; age group 3: 18 to 35 years of age; age group 4: 35 to 54 years of age; age group 5: >54 years of age.

CCI = Charlson comorbidity index; MRI = magnetic resonance imaging.

Primary outcome: sex differences across age groups

In age group 2 “adolescents”, 642 (69.3%) of male patients and 284 (30.7%) of female patients were diagnosed with myocarditis (**Central Illustration**), of which 224 (61.4%) male and 141 (38.6%) female patients were from the Berlin and 418 (74.5%) male and 143 (25.5%) female patients were from the U.S. cohort (**Figures 2A, 2C, and 2D**). Within age group 3 (“young adults”), there were 3,516 (73.8%) male and 1,250 (26.2%) female patients diagnosed with myocarditis, out of which the Berlin cohort was comprised of 1,328 (72.9%) male and 493 (27.1%) female patients, while the U.S. cohort was comprised of 2,188 (74.3%) male and 757 (25.7%) female patients. Sex differences were more balanced in the older age group (age group 5): 808 males (52.8%) vs 722 females (47.2%) in the Berlin cohort and 1,114 (45.8%) males vs 1,316 (54.2%) females in the U.S. cohort. Similar patterns were observed in the biopsy-proven cohort (**Figure 2B**).



Central Illustration

Demographic Characteristics of Acute and Chronic Myocarditis

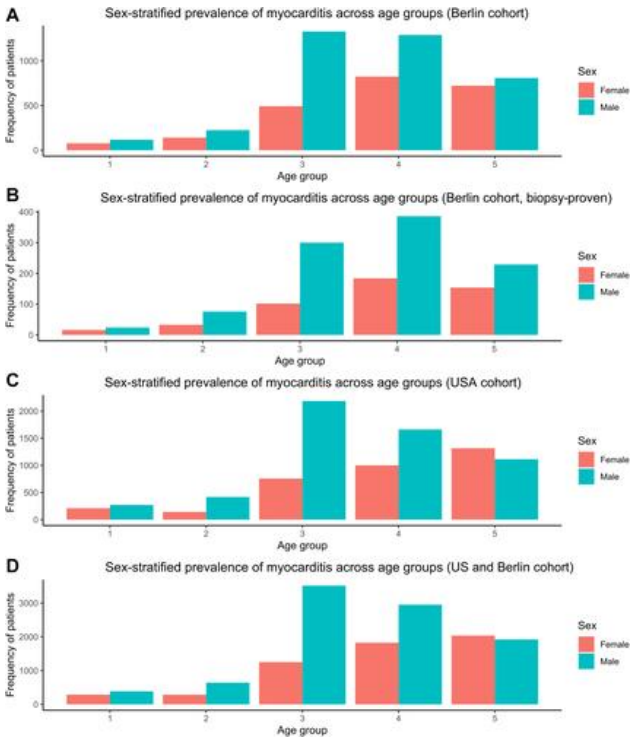


Figure 2

Sex Distribution in Cases of Myocarditis Stratified by Age Groups

(A) Berlin cohort. (B) Patients with biopsy-proven myocarditis in the Berlin cohort. (C) US cohort. (D) Total cohort (Berlin and US). Age group 1: ♀ <11 or ♂ <13 years of age; age group 2: ♀ 11 to 18 or ♂ 13 to 18 years of age; age group 3: 18 to 35 years of age; age group 4: 35 to 54 years of age; age group 5: >54 years of age.

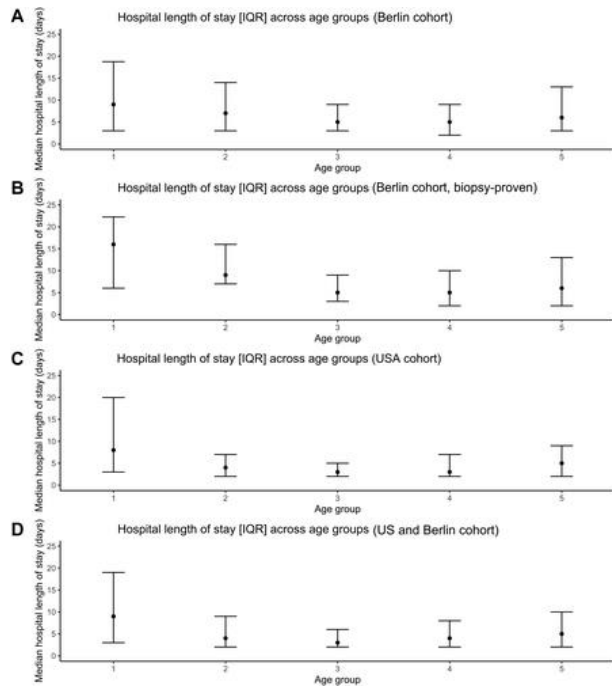


Figure 3

Hospital Length of Stay (IQR) Stratified by Age Groups

(A) Berlin cohort. (B) Patients with biopsy-proven myocarditis in the Berlin cohort. (C) US cohort. (D) Total cohort (Berlin and US). IQR, interquartile range; age group 1: ♀ <11 or ♂ <13 years of age; age group 2: ♀ 11 to 18 or ♂ 13 to 18 years of age; age group 3: 18 to 35 years of age; age group 4: 35 to 54 years of age; age group 5: >54 years of age.

Secondary outcomes: hospital length of stay, hospital mortality, and medical complication rate

Hospital LOS of the youngest (age group 1: 9 [IQR: 3-18] days in the Berlin cohort and 8 [IQR: 3-20] days in the U.S. cohort) and of the eldest patients (age group 5: 6 [IQR: 3-13] days in the Berlin cohort and 5 [IQR: 2-9] days in

the U.S. cohort) were longer compared to the hospital LOS of young adults (age group 3: 5 [IQR: 3-9] days in the Berlin cohort and 3 [IQR: 2-5] days in the U.S. cohort) (**Figures 3A and C**): IRR 1.67 [95% CI: 1.58-1.76], $P < 0.001$ and IRR 1.41 [95% CI: 1.36-1.45] for the Berlin cohort ($P < 0.001$) and IRR 3.38 [95% CI: 3.3-3.47], $P < 0.001$ and IRR 1.39 [95% CI: 1.36-1.42] for the U.S. cohort ($P < 0.001$), respectively. Hospital LOS of age group 4 was similar to age group 3 in the Berlin and the U.S. cohorts, respectively.

Similar patterns were observed for hospital mortality: age group 1 (1.6% in the Berlin cohort and 8.1% in the U.S. cohort) and age group 5 (1.9% in the Berlin cohort and 7.7% in the U.S. cohort) had a higher mortality risk than young adults (age group 3: 0.5% in the Berlin cohort and 2.7% in the U.S. cohort) (**Figures 4A and 4C**): HR: 1.80 [95% CI: 0.34-9.39], $P = 0.487$ and HR: 2.17 [95% CI: 0.79-5.99], $P = 0.135$ for the Berlin cohort, as well as IRR 0.91 [95% CI: 0.62-1.34], $P = 0.65$ and IRR 1.29 [95% CI: 0.99-1.68], $P = 0.063$ for the U.S. cohort, respectively. The hospital mortality rate was also plotted across the continuous patient age in the Berlin and U.S. cohorts (**Supplemental Figure 1**). The largest difference in mortality between male and female patients were observed in age group 2 in the Berlin (0 [0%] male vs 1 [1.4%] female) and U.S. cohort (10 [2.4%] male vs 12 [8.4%] female) (**Supplemental Figure 2**), while there were no sex-based mortality differences in the remaining age groups.

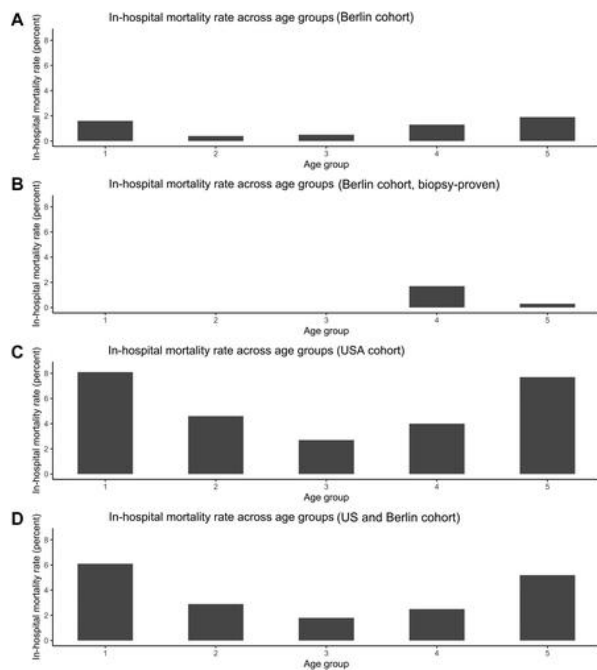


Figure 4

In-Hospital Mortality Stratified by Age Groups

(A) Berlin cohort. (B) Patients with biopsy-proven myocarditis in the Berlin cohort. (C) US cohort. (D) Total cohort (Berlin and US). Age group 1: ♀ <11 or ♂ <13 years of age; age group 2: ♀ 11 to 18 or ♂ 13 to 18 years of age; age group 3: 18 to 35 years of age; age group 4: 35 to 54 years of age; age group 5: >54 years of age.

Causes of death were available for 38 patients in the Berlin cohort (**Supplemental Table 3**). The most frequent causes were circulatory failure in 19 patients (50.0%) and cardiac arrest in 6 patients (15.8%). Of the 38 deceased patients, 10 (26.1%) received an EMB. Myocarditis was diagnosed by EMB in 7 (18.4%) patients, while CMR, clinical or laboratory parameters were used in 29 (76.31%) patients to make the diagnosis of myocarditis (**Supplemental Table 4**). Compared to the U.S. cohort, deceased patients in the Berlin cohort were older (58.5 ± 19.5 vs 46.3 ± 24.5 years), had more comorbidities (Charlson comorbidity index (3 [IQR: 2-6] vs 1 [IQR: 0-2]), a higher percentage of male patients (26 [68.4%] vs 245 [55.8%]), longer hospital LOS (9.5 [IQR: 3.25-29.75] vs 7.0 [IQR: 2-15.5] days), but less frequent medical complications (23 [60.5%] vs 311 [70.8%]) (**Supplemental Table 5**).

With regard to rate of medical complications, there was a similar trend: complications were higher in age group 1 (6.3% in the Berlin cohort and 39.4% in the U.S. cohort) and age group 5 (5.9% in the Berlin cohort and 26.9% in the U.S. cohort) compared to young adults (age group 3: 3.7% in the Berlin cohort and 15.5% in the U.S. cohort) (**Figures 5A and 5C**): OR: 1.89 [95% CI: 1.09-3.16], $P = 0.017$ and 1.87 [95% CI: 1.40-2.50], $P < 0.001$ in the Berlin cohort, as well as OR: 3.55 [95% CI: 2.88-4.36], $P < 0.001$ and OR: 2.01 [95% CI: 1.76-2.3], $P < 0.001$ in the U.S. cohort, respectively. Of note, differences in medical complications were attenuated across age groups in the biopsy-proven myocarditis cohort (**Figure 5B**). Paralleling the pattern in mortality, the most pronounced difference in medical complications between male and female patients was observed in age group 2 in the Berlin (20 (12.5%) male vs 20 (27%) female) and U.S. cohort (74 (17%) male vs 50 (22.1%) female) (**Supplemental Figure 3**). In the remaining age groups, male patients had more frequent medical complications than female patients in the Berlin cohort, while in the U.S. cohort, female patients had more medical complications than male patients. Overall, the mortality rate (1.2% vs 4.8%) and medical complication rate (13.6% vs 22%) were lower in the Berlin cohort compared to the U.S. cohort.

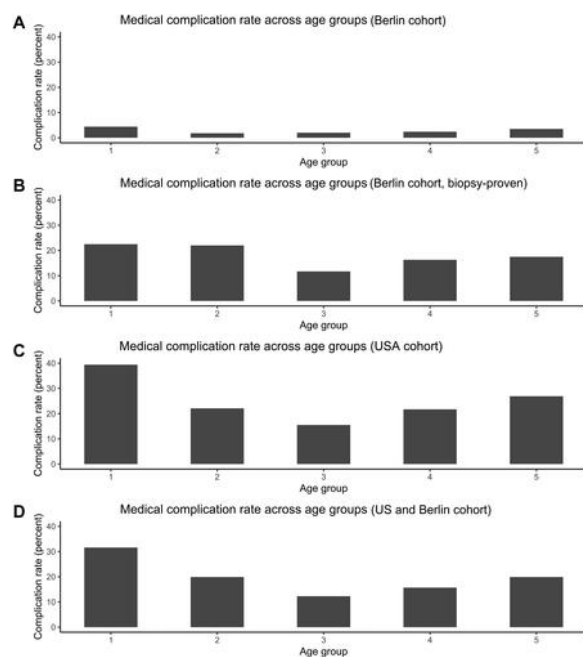


Figure 5

Medical Complication Rate Stratified by Age Groups

(A) Berlin cohort. (B) Patients with biopsy-proven myocarditis in the Berlin cohort. (C) US cohort. (D) Total cohort (Berlin and US). Age group 1: ♀ <11 or ♂ <13 years of age; age group 2: ♀ 11 to 18 or ♂ 13 to 18 years of age; age group 3: 18 to 35 years of age; age group 4: 35 to 54 years of age; age group 5: >54 years of age.

Exploratory analyses in the Berlin cohort

All age groups presented with elevated levels of CRP (26.7 ± 53.1 mg/L) and troponin T (278 ± 958 ng/L) (**Table 2**). In Berlin, the youngest patients had higher levels of leukocytes ($11.4 \pm 4.8/nL$, $P < 0.001$), CRP (29.9 ± 60.0 mg/L, $P = 1.00$), anti-streptolysin antibody (380 ± 555 kU/L, $P < 0.001$), and NT-proBNP ($15,300 \pm 21,700$ ng/L, $P < 0.001$) compared to young adults.

Table 2 Laboratory Values (Within 48 Hours After Hospital Admission) in Patients With Primary Diagnosis of Acute Myocarditis or Acute on Chronic Myocarditis Stratified by Age Group in the Berlin Cohort

	Age Group 1 (n = 194)	Age Group 2 (n = 365)	Age Group 3 (n = 1,821)	Age Group 4 (n = 2,113)	Age Group 5 (n = 1,530)	Total (n = 6,023)
Electrolytes						
Sodium (mmol/L)	137 ± 4.04	139 ± 2.78	139 ± 3.95	139 ± 6.00	139 ± 4.71	139 ± 4.92
Potassium (mmol/L)	4.19 ± 0.567	4.00 ± 0.443	4.06 ± 1.88	4.15 ± 1.55	4.21 ± 0.525	4.13 ± 1.42
Complete blood count						
Hemoglobin (g/dL)	11.7 ± 2.18	14.3 ± 1.45	14.6 ± 1.96	14.3 ± 2.06	13.6 ± 2.25	14.1 ± 2.13

Table 2 Laboratory Values (Within 48 Hours After Hospital Admission) in Patients With Primary Diagnosis of Acute Myocarditis or Acute on Chronic Myocarditis Stratified by Age Group in the Berlin Cohort

	Age Group 1 (n = 194)	Age Group 2 (n = 365)	Age Group 3 (n = 1,821)	Age Group 4 (n = 2,113)	Age Group 5 (n = 1,530)	Total (n = 6,023)
Leukocytes (n/nL)	11.4 ± 4.83	8.75 ± 3.82	8.67 ± 4.00	8.62 ± 4.19	8.55 ± 3.50	8.69 ± 3.99
Renal function						
Creatinine (mg/dL)	0.437 ± 0.207	0.969 ± 1.38	0.906 ± 0.332	0.969 ± 0.450	1.04 ± 0.458	0.952 ± 0.503
Inflammatory markers						
CRP (mg/L)	29.9 ± 60.0	29.4 ± 47.0	29.9 ± 55.9	21.4 ± 47.8	28.9 ± 56.4	26.7 ± 53.1
Procalcitonin (µg/L)	1.65 ± 4.29	0.473 ± 1.03	1.67 ± 10.4	0.627 ± 1.64	2.13 ± 8.74	1.38 ± 7.48
Anti-streptolysin antibody (kU/L)	380 ± 555	118 ± 98.0	152 ± 85.2	151 ± 153	52.6 ± 28.4	176 ± 267
Cardiac markers						
Troponin (ng/L)	225 ± 537	491 ± 1,620	301 ± 713	238 ± 1,000	228 ± 908	278 ± 958
Creatine kinase (U/l)	158 ± 146	380 ± 710	265 ± 417	195 ± 319	231 ± 774	238 ± 529
Myoglobin (µg/L)	271 ± 6.23	241 ± 578	172 ± 534	548 ± 2,930	522 ± 1,430	375 ± 1,850

Table 2 Laboratory Values (Within 48 Hours After Hospital Admission) in Patients With Primary Diagnosis of Acute Myocarditis or Acute on Chronic Myocarditis Stratified by Age Group in the Berlin Cohort

	Age Group 1 (n = 194)	Age Group 2 (n = 365)	Age Group 3 (n = 1,821)	Age Group 4 (n = 2,113)	Age Group 5 (n = 1,530)	Total (n = 6,023)
NT-proBNP (ng/L)	15,300 ± 906	21,700 ± 2,760	± 1,850	± 1,740 ± 5,500	3,630 ± 8,390	2,610 ± 9,480

Values are mean ± SD. Age group 1: ♀ <11 or ♂ <13 years of age; age group 2: ♀ 11 to 18 or ♂ 13 to 18 years of age; age group 3: 18 to 35 years of age; age group 4: 35 to 54 years of age; age group 5: >54 years of age.

CRP = C-reactive protein; NT-proBNP = N-terminal fragment of brain natriuretic peptide.

Additionally, in patients who had a documented transthoracic echocardiogram, LVEF decreased with age: 59.9% ± 11.0% in age group 2 compared to 44.3% ± 16.1% in age group 5 (**Supplemental Figure 4**). Apart from an age-dependent decrease in LVEF, LVEF appeared to be better in younger male patients compared to female patients (age groups 1 and 2). Notably, male patients had a stronger deterioration in LVEF until age groups 3 and 4, such that female patients showed a better LVEF than male patients with older age

Discussion

Myocarditis is defined as inflammation of the myocardium. In developed countries, the most common etiologies of myocarditis are viral infections and autoimmunity, which may result in a broad heterogeneity of clinical symptoms. Patients may report dyspnea and chest pain, while in rare cases, myocarditis may present as potentially life-threatening acute heart failure or cardiogenic shock leading to death.^{23,28} The objective of the present study was

to examine the clinical features of myocarditis in different age groups and to examine differences in sex distribution in 2 large cohorts. In this multicenter cohort study of patients who were treated for a primary diagnosis of acute or chronic myocarditis, the most pronounced differences in sex were observed in patients between the ages of puberty and 54 years. The youngest and eldest patients had the longest hospital LOS and the highest mortality rates compared to young adults, presumably due to more comorbidities and a more complicated clinical disease course.

Sex-based differences in cardiac inflammation

The terms “sex” and “gender” are not interchangeable terms. “Sex” is a biological term based on the patient’s reproductive organs and functions dependent on chromosomal complement.²⁹ Gender describes what a patient identifies as based on social and environmental influences.

In a historic context, myocarditis has been considered a male-predominant disease.³⁰ Multiple trials and registries have confirmed a greater frequency of myocarditis in men than women with a reported sex ratio between 1.5:1 and 1.7:1, which is in alignment with the findings in our study, where the sex ratio was 2.7:1 for the Berlin cohort and 2.9:1 for the U.S. cohort in age group 3—the group with the largest sex difference in frequency.^{7,8,31-35} In accordance with these findings, animal studies have also shown an increased severity of myocarditis in male mice.^{10,36,37} There is increasing clinical and preclinical evidence indicating differential pathogenesis and prognosis of myocarditis between sexes.

Myocarditis is associated with myocardial infiltration of immune cells, predominantly T-cells and macrophages, into the myocardium due to viral or toxic activation of the immune response.³⁸⁻⁴¹ Preclinical models reveal a Th1 vs Th2 dichotomy in adaptive immune responses between both sexes. It has been shown that male mice develop a predominantly Th1-type response, while female mice develop a Th2-type response containing more Foxp3+, Tim-3+, and CTLA4+ regulatory T cell populations.^{10,42-44} Male mice were found to

demonstrate enhanced infiltration by activated M1 and M2b macrophages and mast cells during myocarditis, while females showed increased infiltration by activated M2a macrophages.^{9.45-48} Apart from different immune response patterns between both sexes, cardiac remodeling during myocarditis has also been shown to be sex-dependent. Multiple studies in mice and humans have reported that men with myocarditis have an increased deposition of extracellular matrix proteins and prevalence of myocardial fibrosis compared to women.^{8.14,15,49} Testosterone signaling was shown to be associated with adverse cardiac remodeling, while estrogen signaling appeared to prevent cardiac hypertrophy and fibrosis.^{8.50-52} Furthermore, the severity of myocardial inflammation was shown to be dependent on testosterone and estradiol levels.^{9.43,44,53,54} These findings may explain why we observed a stronger difference in myocarditis frequency in patients between puberty and age 54, indicating an underlying sex hormone-dependent pathogenesis for clinical manifestation of cardiac inflammation.

Health care utilization

The prognosis after myocarditis is dependent on the severity of the cardiac inflammatory process and clinical manifestation of symptoms. Poor prognostic factors have been identified, such as reduced LVEF, left bundle branch block, and syncope.⁵⁵ In our study cohort, patients in age group 2 had an LVEF of 59.9% ± 11%, while patients in age group 5 had a moderately impaired LVEF of 44.3% ± 16.1%.

The youngest and eldest patients in our study cohort were more susceptible to a more severe disease outcome, reflected by an increased frequency of cardiac complications such as cardiogenic shock, cardiac arrest, or ventricular arrhythmias, as well as a higher mortality rate. Cardiogenic shock has been shown to be the most frequent cause of death in patients with myocarditis.⁵⁵ Thus, prolonged hospitalization in both aforementioned age groups could be explained by a higher need for close patient monitoring and comprehensive medical treatment caused by a complex clinical course. Notably, the differences in complication rates between the Berlin and the U.S.

cohorts are remarkable. A probable reason for the observed differences between both cohorts might be the circumstance that highly specialized tertiary care centers from Berlin with capacities for EMBs, CMR examinations, and intensive care unit care were compared to a heterogeneous nationwide data cohort including community and/or rural hospitals in the U.S.

Hospital mortality rates in our study cohort appear to differ from findings in a recent nationwide study in Poland with 3,659 myocarditis patients below the age of 20 years, in which no difference in 30-day mortality between male and female patients was found regardless of the age group.²⁰ Patient selection, which was limited to young patients, may have masked any significant trends in sex differences in the Polish registry study.

Additionally, in our study population, the overall 30-day mortality rate was lower compared to the mortality rate published in the Polish registry study, a U.S.-based registry study (preliminary data from abstract) with 8,875 myocarditis patients, and a Danish registry study with 2,523 myocarditis patients.^{21,22} These data suggest that the prognosis of myocarditis may also be affected by socioeconomic, geographical, and institutional factors. Furthermore, since the analysis of the U.S. database was based on International Statistical Classification of Diseases and Related Health Problems (ICD) codes, while CMR or EMB data were not accessible, some limitations on the accuracy of ICD codes may have to be considered. With regard to hospital LOS, the U.S.-based registry study reported an average LOS of 3 days.²¹ In the Berlin study cohort, the hospital LOS was a function of patient age. Patients in age group 3 had a similar hospital LOS of 5 days, while it was almost doubled in patients in age group 1 (9 days).

Laboratory values

The finding that the youngest age group had the highest levels of leukocytes and CRP is biologically plausible given that immune response mechanisms in general decrease with age due to cellular senescence.⁵⁶ This enhanced

immune response may explain the associated elevation of NT-proBNP in that age group and the more severe clinical course that was observed.

Study Limitations

The strengths of this study include the use of large, multicenter cohorts with a primary diagnosis of myocarditis over a period of 16 years. Patient heterogeneity was reduced by the exclusion of patients with missing information and past medical history of myocarditis. We included granular data on patient characteristics and hospital data, which were manually validated by 4 independent and blinded investigators. However, there are certain limitations to this cohort study. In the Berlin cohort, 25.0% of cases received an EMB, which is considered the diagnostic gold standard. Alternatively, CMR was used in 16.0% of cases in the Berlin cohort. The remaining patients were diagnosed based on clinical symptoms, 12-lead electrocardiogram, and laboratory values, resulting in a less definitive diagnosis. However, data retrieved from biopsy-proven patients were comparable to the overall Berlin cohort indicating high diagnostic accuracy. Additionally, clinical symptoms of included patients, CMR results, severity of disease, and time of myocarditis diagnosis were not retrieved from the data.

Conclusions

In this multicenter study of patients with myocarditis, sex distribution and clinical outcomes varied according to age of the patient. The most obvious differences in sex distribution were observed in age groups between puberty and age 54 years. The youngest and eldest patients had the most severe clinical manifestations of myocarditis with the longest length of stay and the highest rates of in-hospital mortality and cardiac complications. This study highlights the age-dependent features of myocarditis.

16. Spontaneous Coronary Artery Dissection With Concomitant Coronary Vasospasm

A 59-year-old woman was transferred to the emergency department from another hospital because of sudden-onset strong chest pain with ST-segment elevation in leads V₁-V₆ on electrocardiography. She had experienced mental distress for 1 week and was a current smoker with a history of 36 pack-years. Her blood pressure was 138/87 mm Hg, heart rate was 60 beats/min, and oxygen saturation was 98%. Physical examination revealed no cardiac murmur or abnormal lung sounds.

Learning Objectives

- To recognize the possibility of coexisting VSA in cases of SCAD with intracoronary imaging.
- To understand the utility of provocative coronary vasospasm testing for diagnosing concomitant VSA in post-SCAD patients.
- To learn an optimal therapy for preventing recurrence in patients with SCAD and VSA.

Medical History

The patient had no medical history.

Differential Diagnosis

The initial differential diagnoses included acute coronary syndrome, acute aortic dissection, acute myocarditis/pericarditis, and Takotsubo cardiomyopathy.

Investigations

Electrocardiography showed ST-segment elevation in leads V₁-V₆. Laboratory examination demonstrated an elevated troponin T concentration of 0.150

ng/mL (reference range: ≤ 0.014 ng/mL) and normal creatine kinase concentration (142 U/L). Chest radiographs showed no abnormalities. Transthoracic echocardiography exhibited apical hypokinesis with a preserved left ventricular ejection fraction. These abnormalities supported a working diagnosis of acute coronary syndrome, and emergency cardiac catheterization was performed.

Management

Emergency coronary angiography after intracoronary administration of isosorbide dinitrate revealed an occlusion of the mid left anterior descending artery (LAD) (**Figure 1A, Video 1**). No significant stenosis was present in the right coronary artery. The patient was diagnosed with ST-segment elevation myocardial infarction (STEMI) and immediately underwent percutaneous coronary intervention (PCI). A guidewire with a microcatheter was smoothly advanced into the distal LAD, and coronary blood flow was restored to thrombolysis in myocardial infarction grade 2 (**Videos 2 and 3**). Optical frequency domain imaging (OFDI) revealed an intimal tear in the distal LAD, vasa vasorum proliferation in the mid-to-distal LAD, and medial dissection in the mid LAD (**Figure 1B to 1G, Video 4**). There was no atherosclerotic plaque in the mid-to-proximal LAD (**Figure 1H, Video 4**), suggesting that the etiology of STEMI was type 4 spontaneous coronary artery dissection (SCAD) due to a total occlusion at the initial angiography. Given the disturbed coronary flow, a drug-eluting stent was deployed to cover the severely distorted segment (**Figure 2A**). The intimal tear was treated conservatively because of the small and tortuous vessel. OFDI displayed the stent covering almost part of the medial dissection, and the residual uncovered dissection did not require additional stent deployment due to thrombolysis in myocardial infarction grade 3 blood flow (**Figure 2B, Videos 5 and 6**). The maximum postprocedural creatine kinase concentration was 780 U/L, and intravenous administration of heparin and nicorandil was continued. On hospital day 4, chest pain with mild ST-segment elevation suddenly occurred after the discontinuation of nicorandil and was completely relieved immediately after sublingual administration of nitroglycerin. This episode suggested a

complication of vasospastic angina (VSA), and, after the initiation of a calcium channel blocker (benidipine 4 mg), the chest pain did not recur. Cardiac computed tomography on hospital day 11 revealed preserved coronary flow in the LAD, and the patient was discharged on hospital day 13. She remained asymptomatic with cessation of smoking and treatment with calcium channel blocker. Three months after the initial hospitalization, repeat coronary angiography performed to investigate VSA showed partial restoration of the SCAD in the LAD (**Figure 3A, Video 7**). An acetylcholine provocation test also revealed diffuse stenosis of the mid-to-distal LAD with chest pain and terminal T-wave inversion in leads II, III, aVF, and V₃-V₆ (**Figure 3B, Video 8**), which was completely restored after intracoronary isosorbide dinitrate (**Figure 3C, Video 9**). OFDI in the LAD displayed resolution of the intimomedial dissection and medial thickening, mild stent malapposition, and mild tissue growth in the proximal edge of the stent (**Figure 4A to 4C, Video 10**). The patient remained asymptomatic more than 1 year after the initial hospitalization.

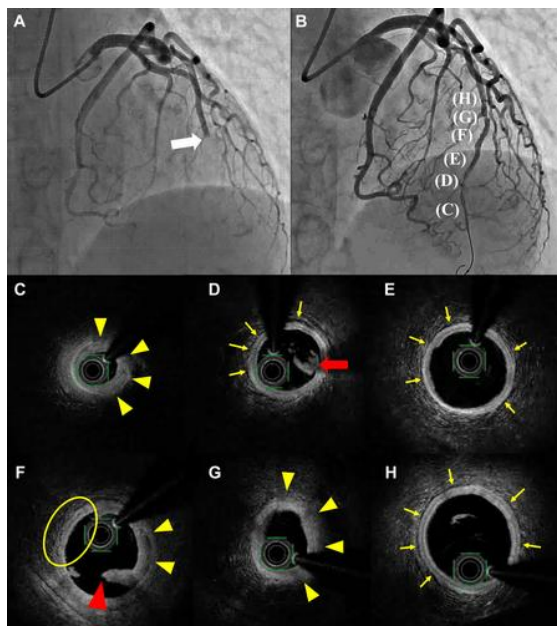


Figure 1

Emergency Left Coronary Angiography and OFDI of LAD at Initial Admission

(A) Total occlusion of the mid LAD (white arrow). (B) OFDI of the LAD after recanalization, demonstrating (C) medial thickening at the far distal site (yellow arrowhead), (D) an intimal tear at the distal LAD (red arrow) with enhanced vasa vasorum formation (yellow arrows), (E) vasa vasorum proliferation (yellow arrows) in the mid-to-distal LAD, (F) medial dissection (red arrow) with concomitant medial thickening (yellow arrowheads) and increased microvessels (yellow circle) in the mid LAD, (G) medial thickening at the proximal site of the dissection (yellow arrowheads), and (H) a healthy coronary artery with enhanced vasa vasorum formation (yellow arrows) in the mid-to-proximal LAD. LAD = left anterior descending artery; OFDI = optical frequency domain imaging.

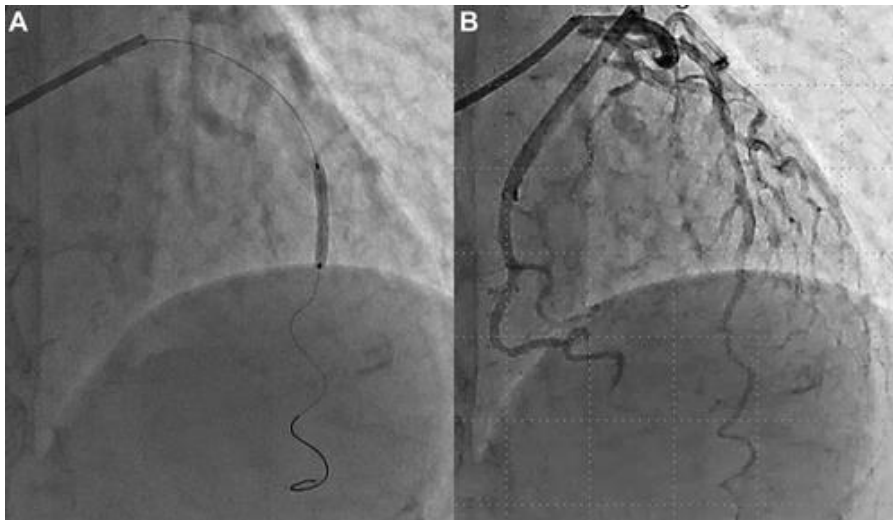


Figure 2

Emergency Revascularization of Culprit Lesion

(A) A drug-eluting stent was deployed to cover the severely distorted segment. (B) Final angiography revealed restoration of coronary blood flow to the distal LAD. Abbreviation as in **Figure 1**.

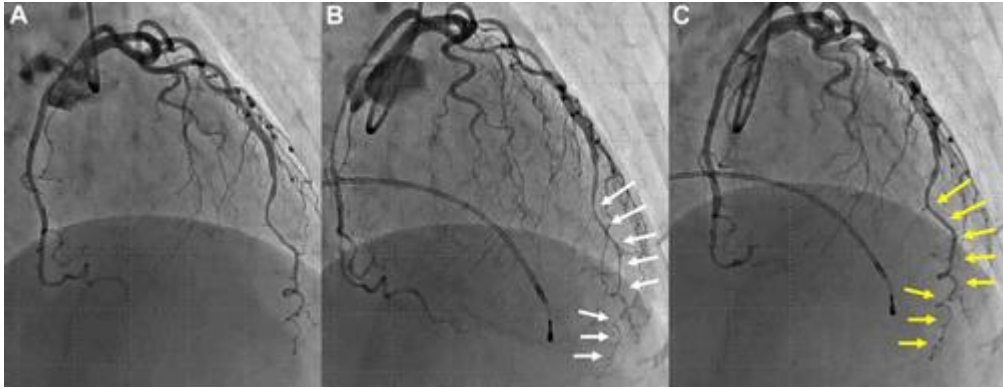


Figure 3

Acetylcholine Provocation Test 3 Months After Prior Myocardial Infarction

(A) Left coronary angiography showing partial restoration of the dissection of the LAD. (B) Acetylcholine provocation test revealing diffuse stenosis of the mid-to-distal LAD (white arrows). (C) Complete restoration of vasospasm after intracoronary isosorbide dinitrate (yellow arrows). Abbreviation as in **Figure 1**.

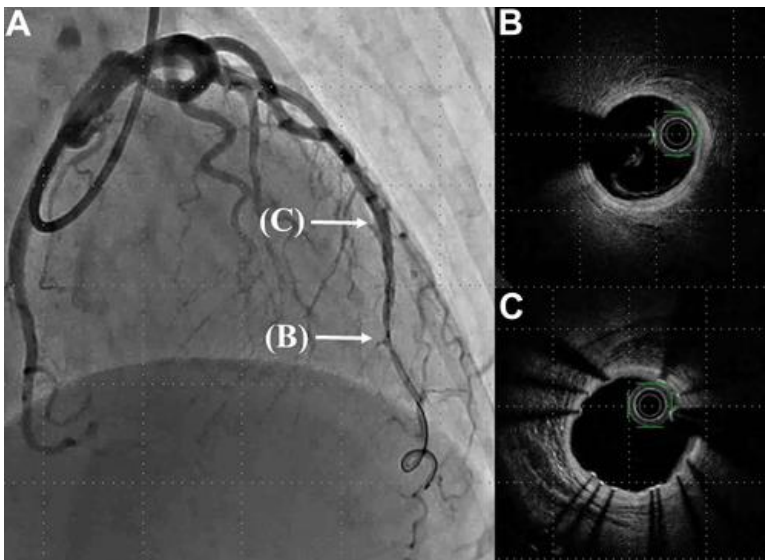


Figure 4

OFDI in LAD 3 Months After Initial Hospitalization

(A) Follow-up OFDI in the LAD, displaying (B) resolution of the intimal tear and (C) the medial dissection covered with a stent. Abbreviations as in **Figure 1**.

Discussion

SCAD is a rare cause of myocardial infarction and mainly affects women.¹ According to multicenter registries, 26.8% of SCAD patients are type 4, characterized by complete occlusion due to intramural hematoma and predominantly presenting with STEMI,² which is challenging to diagnose without intracoronary imaging. Most patients are treated conservatively, whereas patients with ongoing ischemia undergo PCI,¹ as in the present case.

VSA is characterized by hyper-reactivity of coronary vascular smooth muscle cells and endothelial dysfunction.³ The acetylcholine provocation test is the gold standard for diagnosing VSA.³ However, recent technical advancements in intracoronary imaging have revealed VSA-specific morphologic findings including enhanced adventitial vasa vasorum formation and intraplaque neovessels,⁴ medial thickening, and layered plaque,³ which could help identify episodes of VSA. In this case, OFDI during the primary PCI demonstrated coronary artery dissection with these VSA-specific features (**Figures 1C to 1H**). Although these imaging characteristics, particularly medial thickening, should be cautiously interpreted in the acute phase of SCAD due to some biases generated from the primary parietal bleeding in the adventitia and media, intracoronary imaging in this case suggested coexisting VSA in the culprit LAD and highlighted the need for vasoreactivity study.

Several cases of SCAD complicated by VSA have been reported.^{5,6} In fact, SCAD and VSA may share certain risk factors, including middle age, emotional stress, and endothelial dysfunction.⁷ However, few studies have confirmed vasospasm in the culprit vessel of SCAD by vasoreactivity test. In a previous study involving the ergonovine provocation test in 11 patients with a history of SCAD, only 1 patient had a positive vasospasm response in the culprit vessel.⁵ Another study demonstrated that the coronary epicardial and

microvascular responses to acetylcholine, adenosine, and nitroglycerine were comparable between patients with and without SCAD.⁸ These results suggest that coronary epicardial and microvascular vasomotor dysfunction may not be a predominant feature of SCAD; however, a complication of VSA could manifest as a phenotype of SCAD. Such patients might ideally be treated using calcium channel blockers because β blockers, predominantly prescribed in patients with SCAD,¹ may lead to worsening of coronary vasoconstriction in patients with VSA. Accordingly, clinicians should consider the possibility of coexisting VSA in patients with SCAD and investigate VSA using coronary vasospasm testing in suspicious cases, which requires further investigation.

Follow-up

The patient remained free of symptoms and cardiovascular events with long-term administration of calcium channel blocker for more than 1 year after the prior STEMI.

Conclusions

SCAD can coexist with VSA because of several shared risk factors. Given the need for different clinical management strategies, clinicians should recognize that SCAD can be complicated by VSA.

17. Women With Depression May Face Higher CV Risk Than Men

People with depression face an increased risk of cardiovascular disease; however, more women experience cardiovascular disease following a depression diagnosis than men, according to a new study published today in *JACC: Asia*. The study investigates the connection between depression and cardiovascular disease, shedding light on potential mechanisms that contribute to its sex-based differences and underscoring the importance of tailoring cardiovascular disease prevention and management strategies according to sex-specific factors.

Keitaro Senoo, MD, et al., evaluated the association between depression and subsequent cardiovascular disease events by conducting a retrospective analysis using data collected between 2005 and 2022 in the JMDC Claims Database in Japan. They identified 4,125,720 participants who met the study's criteria. The median age was 44 (36-52) years, and 1,754,734 participants were women. Depression was defined as those clinically diagnosed before their initial health checkup.

Using standardized protocols, the study collected participant's body mass index, blood pressure and fasting laboratory values at their initial health checkup. The primary outcome was a composite endpoint including myocardial infarction (MI), angina pectoris, stroke, heart failure (HF) and atrial fibrillation (AFib).

Researchers analyzed the statistical significance of differences in clinical characteristics between participants with and without depression. Results indicate that the hazard ratio of depression for cardiovascular disease was 1.39 in men and 1.64 in women compared with participants without depression. Models also indicate that hazard ratios of depression for MI, angina pectoris, stroke, HF and AFib were higher for women than for men.

Study authors highlight an important discussion regarding the potential mechanisms that may contribute to why depression impacts women's heart health more than men's. One explanation is that women may experience more severe and persistent symptoms of depression compared to men, and they may be more likely to have depression during critical periods of hormonal changes, such as pregnancy or menopause.

Other mechanisms include women's greater susceptibility to traditional risk factors when depressed, such as hypertension, diabetes and obesity, which may contribute to the development of cardiovascular disease. Differences in health care utilization and treatment between men and women and sex-specific differences in biological factors, such as genetics and hormonal profiles, may also increase women's cardiovascular disease risk.

“Our study found that the impact of sex differences on the association between depression and cardiovascular outcomes was consistent,” said **Hidehiro Kaneko, MD**, an author of the study. “Health care professionals must recognize the important role of depression in the development of cardiovascular disease and emphasize the importance of a comprehensive, patient-centered approach to its prevention and management. Assessing the risk of cardiovascular disease in depressed patients and treating and preventing depression may lead to a decrease of cardiovascular disease cases.”

18. Intraoperative Anemia Mediates Sex Disparity in Operative Mortality After CABG

BACKGROUND

Women undergoing coronary artery bypass grafting (CABG) have higher operative mortality than men.

OBJECTIVES

The purpose of this study was to evaluate the relationship between intraoperative anemia (nadir intraoperative hematocrit), CABG operative mortality, and sex.

METHODS

This was a cohort study of 1,434,225 isolated primary CABG patients (344,357 women) from the Society of Thoracic Surgeons Adult Cardiac Surgery Database (2011-2022). The primary outcome was operative mortality. The attributable risk (AR) (the risk-adjusted strength of the association of female sex with CABG outcomes) for the primary outcome was calculated. Causal mediation analysis derived the total effect of female sex on operative mortality risk and the proportion of that effect mediated by intraoperative anemia.

RESULTS

Women had lower median nadir intraoperative hematocrit (22.0% [Q1-Q3: 20.0%-25.0%] vs 27.0% [Q1-Q3: 24.0%-30.0%], standardized mean difference 97.0%) than men. Women had higher operative mortality than men (2.8% vs 1.7%; $P < 0.001$; adjusted OR: 1.36; 95% CI: 1.30-1.41). The AR of female sex for operative mortality was 1.21 (95% CI: 1.17-1.24). After adjusting for nadir intraoperative hematocrit, AR was reduced by 43% (1.12; 95% CI: 1.09-1.16). Intraoperative anemia mediated 38.5% of the increased mortality risk associated with female sex (95% CI: 32.3%-44.7%). Spline regression showed a stronger association between operative mortality and nadir intraoperative hematocrit at hematocrit values $<22.0\%$ ($P < 0.001$).

CONCLUSIONS

The association of female sex with increased CABG operative mortality is mediated to a large extent by intraoperative anemia. Avoiding nadir intraoperative hematocrit values below 22.0% may reduce sex differences in CABG operative mortality.

19. LE8 Can Improve Future Heart Health in Women With History of Complicated Pregnancy

Among women with a history of adverse pregnancy outcomes (APOs), maintaining better cardiovascular health is associated with a significantly lower risk for incident cardiovascular disease (CVD), according to a study presented at the American Heart Association Epidemiology and Prevention/Lifestyle and Cardiometabolic Health 2024 Scientific Sessions, held from March 18 to 21 in Chicago.

Frank Qian, M.D., M.P.H., from the Boston University Chobanian & Avedisian School of Medicine, and colleagues evaluated the association between Life's Essential 8 (LE8) and incident CVD in women with a history of APOs. The analysis included 2,263 participants with a prior diagnosis of an APO (e.g., hypertensive disorders of pregnancy, gestational diabetes, placental abruption, small for gestational age, or preterm birth) and 107,260 parous participants without a history of APOs, all free from CVD at baseline.

The researchers found that at a mean 13.5 years of follow-up, compared with women in the bottom tertile of the LE8 score, those in the top tertile had a lower incidence of total CVD, coronary heart disease, and atrial fibrillation. There was a significant interaction observed between a history of APOs, LE8 score, and incident CVD. Women with a prior APO who maintained a high LE8 score had a similar CVD risk as those without APO with a high LE8 score. However, excess CVD risk was seen for women with intermediate or low LE8 scores.

"We need to encourage health care professionals to integrate Life's Essential 8 into clinical practice to improve heart health in women with and without pregnancy-related disorders," Nieca Goldberg, M.D., an American Heart Association volunteer expert not involved with the study, said in a statement.

20. Men, Women Have Different Factors Tied to Increased Frailty in Older Age

There are some common factors among women and men that are associated with increases in frailty components, as well as notable sex differences, according to a study recently published in the *Archives of Gerontology and Geriatrics*.

Dayane Capra de Oliveira, Ph.D., from the Federal University of Sao Carlos in Sao Paulo, Brazil, and colleagues analyzed sex differences in factors associated with the increase in the number of frailty components. The analysis included 1,747 participants (aged 60 years and older) with 12 years of follow-up data as part of the ELSA study.

The researchers found that the increase in the number of frailty components in both sexes was associated with an advanced age (70 to 79 years and ≥ 80 years and older), low educational level, sedentary lifestyle, elevated depressive symptoms, joint disease, high C-reactive protein levels, perception of poor vision, and uncontrolled diabetes. In men, osteoporosis, low weight, heart disease, living with one or more people, and perception of poor hearing were associated with an increase in the number of frailty components. For women, high fibrinogen concentration, controlled diabetes, stroke, and perception of

fair vision were associated with an increase in the number of frailty components. There was a lower increase in the number of frailty components among obese women and men and overweight women versus those in the ideal weight range.

"Our main findings showed that despite some common factors in women and men being associated to increases in frailty components, there were important sex differences that should be considered during clinical assessment," the authors write.